

# Univariate Solutions in a Multivariate World: Can We Afford to Practice as in the “Good Old Days”?

Laurence F. McMahon, Jr, MD, MPH; Rodney Hayward, MD; Sanjay Saint, MD, MPH;  
Michael E. Chernew, PhD; and A. Mark Fendrick, MD

“Healthcare costs continue to rise and are approaching a crisis.” This oft-repeated refrain appears in both popular and professional media and commentaries. However, the cost-containment discussion thus far has failed to acknowledge in any substantive way the role physicians play in driving the escalation. More importantly, the discussion has not attempted to constructively engage the profession in formulating clinically appropriate solutions.

Approximately 50% of the increased cost of healthcare is attributable to novel applications of “technology,” defined broadly to include innovations in healthcare from pharmaceuticals to surgery.<sup>1,2</sup> Historically, investment in innovative technology has led to a rising proportion of our gross domestic product being devoted to healthcare. Dollars spent on healthcare are *not* spent in other economic sectors. These trade-offs, while rarely explicit, are real: witness the budget debates in state legislatures as they confront cutting Medicaid or school programs in response to declines in state income. Furthermore, the higher cost health system that results from additional use of medical technology leads to more costly health insurance. Rising premiums account for much of the increase in the numbers of uninsured.<sup>3</sup>

While society and the medical profession have embraced technology as a means to improve our collective health, they have rarely done so after a critical analysis of either cost or efficacy of the technology.<sup>4</sup>

This bleak scenario is largely mutable. Traditional risk-benefit analysis of medical advances must evolve to assess whether the overall effects aid our patients, and more importantly, which of our patients are most benefited. In addition, we must harness new information technology, now used largely for document storage and results reporting, to make more effective clinical judgments.

## Changing the Paradigm

The modern approach to medical practice is often described as resting on dual footings. The first is exemplified by John Snow’s removal of the Broad Street pump handle, which curtailed the London cholera outbreak in 1854.<sup>5</sup> The second is Koch’s Postulates, which

emphasize the identification of an organism’s direct association with a disease, the isolation of that organism, and the subsequent infection with the organism of a healthy animal. Each of these foundations emphasizes a univariate cause and effect model. Univariate approaches explain a decreasing proportion of the problems facing medicine and healthcare, including risk-benefit analysis. “Risk stratifying” patients and populations can greatly assist us in directing our innovations to those subgroups that are most likely to benefit.

## The Gold Standard—Fool’s Gold?

The prevailing univariate approach to assess risk and benefit, in part, stems from some key assumptions in our prevailing gold standard—the double-blinded, randomized, controlled clinical trial (RCT). The standard clinical trial is often portrayed as reflecting an orthodox set of assumptions: first, the risk of developing the study condition is relatively constant among those enrolled in the study; and second, the benefit obtained from the treatment is relatively equally distributed across all study subjects. cursory review of the literature demonstrates these assumptions are rarely true. Although explicit attempts are made to limit clinical variability among study subjects, substantial variation almost always remains. This risk heterogeneity can only be assessed when multiple dimensions are considered simultaneously (eg, age, sex, prior history of important event, etc). Patient heterogeneity is a concept that practicing physicians understand and employ daily in patient care.

As actual study populations differ from the ideal research design, the apparent benefit will be predictably over- or underestimated. Absolute benefit, in contrast to relative benefit, is often concentrated in the highest risk subset of the study population. Therefore, the group with the highest risk experiences most of the benefit

From the Department of Internal Medicine, University of Michigan, Ann Arbor (all); Ann Arbor VA Health Services Research and Development Field Program (RH, SS); Department of Health Policy and Management, University of Michigan School of Public Health, Ann Arbor (LFM, RH, MEC, AMF); and Patient Safety Enhancement Program, University of Michigan Health System (SS).

Address correspondence to: Laurence F. McMahon, Jr, MD, MPH, University of Michigan Health System, 300 North Ingalls, Suite 7C27, Ann Arbor, MI 48109-0429. E-mail: lmcMahon@umich.edu.

and, on a population basis, often accounts for most of the potential benefit from treatment. In contrast, those patients with average or low risk often receive little absolute benefit, while accounting for most of the costs.<sup>6-8</sup> The proportion of patients in a population that segregates into a high-risk/high-benefit group, or a lower-risk/lower-benefit group, will determine the apparent overall population-based clinical effectiveness and cost effectiveness. We can no longer tolerate “averages,” and their resulting over- and undertreatment patterns, when we have the technical capacity to use multi-variable prediction models to more precisely estimate a patient’s actual risk and benefit.

### **Examples of Risk Stratification: Impact on Benefits**

Standard clinical trial reporting usually identifies univariate risk adjustments to determine their impact on randomization, for example, gender, prior clinical history, and age. Unfortunately, RCTs seldom account for multivariate risk adjustment, which may dramatically impact the assessment of a patient’s underlying risk, as well as the true benefit of an intervention.

One of the most widely publicized and well-designed clinical trials in recent years was the GUSTO study.<sup>9</sup> This study found a moderate benefit of t-PA therapy over streptokinase in patients with acute myocardial infarction. A recent analysis, using a multivariate risk adjustment model, demonstrated that GUSTO subjects had varied substantially in their risks of complications and death.<sup>10</sup> The population with the lowest quartile of predicted benefit, defined using a multivariate risk-benefit model, received net harm from the use of t-PA vs streptokinase, because of the higher risk of bleeding associated with t-PA. Thus, while “on average” t-PA had a moderate benefit, the benefit ranged from a highly significant mortality benefit in the highest risk-benefit quartile of patients to net harm in the lowest risk-benefit quartile of patients.<sup>10</sup>

Segregation of risk and benefit is a regular part of practice in some spheres, such as cancer treatment, where we do not usually give the same treatments to patients with stage 4 disease as to those with stage 1 disease. Yet this approach is largely disregarded in other realms, particularly when the main “costs” of treatment are patient inconvenience, side effects, or economic costs. For example, most professional organizations recommend the same level of tight control for almost all individuals with diabetes. However, patients with earlier onset experience dramatically greater risk of microvascular complications from hyperglycemia than those with later onset.<sup>11</sup> Because about 80% of the

risk of serious diabetic complications is clustered in 15% to 20% of patients, 1-dimensional recommendations can result in significant over-treatment of low-risk patients, or directing too little attention and resources to high-risk patients, or both.<sup>11</sup> While risk stratification has been adopted, to notable effect, in hyperlipidemia treatment and revascularization recommendations, simplistic “one size fits all” or “treat the number” recommendations still predominate. Clinical guidelines and quality improvement programs devote scant attention to closer and more frequent follow-up for high-risk patients, resulting in the modern medical phenomenon of more care and lower quality.<sup>12,13</sup>

### **Targeting our Efforts**

Disease-specific advocates may argue that multivariate risk assessment is a thinly disguised brief for cost containment. We suggest it is a necessary paradigm shift. If a health system is responsible for caring for 1000 patients with diabetes, more good will be accomplished if 50 higher-risk patients receive close eye care follow-up than if 700 to 800 low-risk patients meet current “one size fits all” retinal screening quality standards.<sup>14,15</sup> Given our current market-based focus on performance standards, it is not surprising that most healthcare systems spend greater resources ensuring that all patients with diabetes have annual eye examinations and urine protein screening than on intensive follow-up of high-risk patients with diabetes and known retinopathy.<sup>14-17</sup> Similarly, aggressive treatment of hypertension and intensive glycemic control for those with early-onset diabetes have not been targeted by performance measures, despite the proven benefit of these measures to substantially reduce overall morbidity and mortality.<sup>17</sup>

Risk stratification methods are just as applicable in emerging technologies. Vascular catheter-related infection, a common and costly event for inpatients, illustrates this point well.<sup>18</sup> The use of catheters coated with antiseptic agents significantly decreases the risk of catheter-related bloodstream infection (by approximately 40%, on average), compared with standard catheters, in patients catheterized for between 2 and 10 days.<sup>9</sup> It is far more cost effective, however, to use these higher cost antiseptic catheters in high-risk populations (patients who are critically ill or severely immunocompromised) than in the more prevalent “low-risk” group (such as patients requiring central venous access for only a short period of time).<sup>19</sup>

### **Barriers to Change**

Both intrinsic and extrinsic factors have impeded our ability to inculcate multivariate risk subsetting of

patients to guide our assessment of new clinical interventions and prevention and treatment strategies, and to modify payment and benefit strategies. Perhaps the most difficult intrinsic barrier is that physicians have been conditioned to think in a univariate linear mode, exemplified by Snow and Koch. The clinical complexity of medicine today and increasing costs paired with decreased therapeutic margins no longer support this simplistic view.

A second barrier is the medical marketplace. The majority of important clinical trials now are supported by for-profit companies. Their goals are to bring new, profit-generating treatments to the market. In most instances in which a product would benefit, even marginally, a group of patients, multivariate population assessment would lower the product's market share, thus transforming a potential "blockbuster" into a "niche" product. It is clearly counter to the sponsor's financial interest in such instances to engage in multivariable risk-benefit analysis.

A third barrier, tangential to the profession, is created by accrediting organizations. These organizations provide simple, straightforward quality improvement benchmarks for physicians and health systems. The standards have largely followed recommendations from the profession, which suffer from the same deficiencies in simplistic, averaged benefit assessment modeling. For example, the National Committee for Quality Assurance (NCQA) measures health plan quality using indicators such as the proportion of patients with diabetes who obtain yearly retinal examinations. This metric encourages wasteful resource utilization; patients whose last examination was normal receive little benefit from yearly examinations, while patients most likely to benefit from intensive screening regimens may be adversely affected if their access is impeded by the large demand for low-yield examinations.<sup>14-17</sup> This external standard, imposed on many managed care organizations, leads to wasteful care and has the potential for less benefit at a population level than would be the case if the same (or fewer) resources were directed to the highest risk group of patients.<sup>16,17</sup>

### Solutions

We must re-educate our profession to the consequences of practicing medicine using the outdated univariate paradigm. We must start by re-analyzing important clinical trials.<sup>6,7,10</sup> The simplistic clinical recommendations stemming from such trials can be contrasted with much richer, individualized recommendations based on multivariate risk assessment. Many trials have the statistical power to allow a multivariate analysis without concern of embarking on a "fishing expedition."<sup>6,10</sup> Second, we must begin to use

information technology to understand better the risks our patients face, based on a multivariate assessment of their clinical condition, and coupled with a better assessment of treatment and its impact. Third, we must require higher standards in the analysis of future clinical trials. The profession must create these standards, which can be amplified and disseminated through professional journals. Sadly, given the current for-profit funding source of clinical research, the noted conflicts of interest, and the opportunity cost presented by for-profit organizations, it is less likely that a transition to multivariate analysis will occur spontaneously among clinical investigators.

Finally, we must begin to use economic tools to innovatively maximize and enhance care. For example, copayments have traditionally been based on the acquisition cost of the intervention/product rather than on its cost effectiveness. A new concept, benefit-based copay,<sup>20</sup> attempts to identify an individual's inherent risk (risk stratification) of developing adverse outcomes, as well as the potential benefit to be gained from a medical intervention, treatment, or preventive service. Accordingly, patients at high risk of developing diabetic retinopathy may have no copayment for yearly or even more frequent screening. Conversely, a patient with diabetes and little or no risk of developing diabetic retinopathy in the short-term might retain a copayment for that service. Finally, a health organization that had close to 100% of its *high-risk* patients with diabetes receiving yearly retinal examinations should receive a higher performance score than a competitor with an equally high percentage of low-risk patients with diabetes obtaining such services.

### Conclusions

Instituting economically sound, methodologically rigorous, and clinically advantageous approaches to the financial challenges encumbering our healthcare system may provide solutions. However, these approaches require us to alter our prevailing univariate paradigm, to revisit how we interpret data from clinical trials, and how we interact with both the funders of these trials and their publishers. We must also recalibrate the metrics used to assess population-based markers of health system success. This transformation is in the best interest of the profession, our society, and our patients. We must begin to use the tools at hand to improve the care of our patients, to be responsible stewards of the profession, and to wisely utilize the resources entrusted to us by society.

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