Looking for the Outcomes We Love in All the Wrong Places: The Questionable Value of Biomarkers and Investments in Chronic Care Disease Management Interventions

Frederic R. Curtiss, PhD, RPh, CEBS, and Kathleen A. Fairman, MA

According to Roman mythology, a handsome but vain young man, Narcissus, became thirsty while hunting in the woods. Kneeling down upon the banks of a stream, he became fascinated by his own reflection. Refusing to drink the water lest he damage the lovely image in the stream, and not realizing that he was in fact staring only at a reflection of himself, he eventually died of thirst. The tragic error of Narcissus was looking in the wrong place to meet his needs.1

Events of the past 2 years have, in sometimes disconcerting ways, demonstrated that “evidence-based” medicine has been looking in the wrong places to meet many of the most important needs of the patients it serves. The results of 4 recent large clinical trials have highlighted the limitations of conventional wisdom regarding the value of key biomarkers in predicting clinical end points, and preliminary evaluation of the Medicare Health Support (MHS) demonstration project, a randomized trial of disease management interventions that had been touted by proponents as a way to “prove that disease management can be cost-effective at a national level with a Medicare population,”2 instead produced the disappointing finding in June 2007 that the fees paid to participating vendors had “far [exceeded] savings produced.”3 In 2008, the Centers for Medicare & Medicaid Services (CMS) announced that it would terminate the MHS demonstration for failure to meet the statutory requirements necessary for its continuation, most prominently, programmatic cost savings.4 Conventional wisdom was also challenged recently when 2 Milliman Research Reports showed that (a) medical care cost increases for Medicare beneficiaries with chronic disease have been lower than the cost increases for beneficiaries without chronic disease, and (b) spending on wellness programs and chronic care management is unlikely to generate a favorable return on investment. These developments and the facts in evidence shake the foundation of many managed care interventions.

Fitch et al. in a Milliman research report informed us that the cost increases for the nonchronic Medicare fee-for-service (FFS) population have been higher over the 4-year period ended in 2006 than the cost increases for 5 chronic conditions: coronary artery disease (CAD, including angina), diabetes, chronic obstructive pulmonary disease (COPD), congestive heart failure (CHF), and asthma.5 The annual per-member cost increase for Medicare FFS beneficiaries with chronic disease have been lower than the cost increases for beneficiaries without chronic disease, and spending on wellness programs and chronic care management is unlikely to generate a favorable return on investment. These developments and the facts in evidence shake the foundation of many managed care interventions.

<table>
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<tr>
<th>TABLE</th>
<th>Annual PMPM Increases in Medicare Expenditures by Chronic Condition</th>
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<tbody>
<tr>
<td>CAD</td>
<td>4.2%</td>
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<tr>
<td>Diabetes</td>
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<td>COPD</td>
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<td>CHF</td>
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<td>Asthma</td>
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<td>Chronic overall</td>
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<td>Nonchronic</td>
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However, annual cost increases do not tell the entire story. Medicare beneficiaries with chronic diseases had about 4 times higher per member per month (PMPM) costs compared with nonchronic disease beneficiaries over the 4-year period ended in 2006. Medicare FFS beneficiaries with chronic diseases in 2006 had average PMPM costs of $1,473 versus $410 for beneficiaries without chronic diseases. This imbalance in average cost per beneficiary means that while chronic disease beneficiaries accounted for 33.7% of the entire Medicare population in 2006, they accounted for 64.6% of total Medicare allowed spending. Still, the sustained rate of increase for the beneficiaries without chronic disease is not an expected finding.

What to Expect from Wellness and Disease Management Programs

In 2003, Sandra Foote, then Director of the Health Insurance Reform Project at George Washington University, advocated rigorous tests of the effectiveness of population-based disease management programs in improving care for chronic diseases within Medicare.6 Foote’s argument that disease management pilot projects “could act as a catalyst for improving the health of chronically ill beneficiaries” was based on the common-sense idea that disease management programs might “help beneficiaries and providers increase their adherence to evidence-based guidelines.”
Bolstered by testimony of then-Director of CMS, Daniel Crippen, that 88% of Medicare spending was attributable to enrollees with 3 or more chronic conditions,8 Foote’s argument was viewed by observers as “convincing” and consistent with available evidence at the time.8 Yet, much to their credit, both Foote and Crippen pointed out in 2003 that the evidence in favor of disease management’s effectiveness was derived largely from methodologically weak, nonrandomized studies whose results were vulnerable to the effects of selection bias (e.g., more motivated or healthier individuals attracted to participation in a disease management program) and regression to the mean, the phenomenon by which higher-cost patients tend to incur lower costs over time without any intervention.

The sharp contrast between the early high hopes for disease management’s potential to improve quality and reduce costs and the lackluster MHS results provides a case study in what happens when the pace of an innovation’s development, based on a combination of weak research evidence and overreliance on intermediate measures of care rather than on end point outcomes, outstrips the availability of solid research to guide an evidence-based approach. The MHS dénouement was not entirely unexpected by those familiar with the limitations and findings of the disease management research literature. In a textbook example of regression to the mean, Rubin et al.’s 1998 study of a comprehensive diabetes care management program claimed gross savings of $50 per diabetic patient per month and a 21% reduction in hospital bed days, based solely on a comparison of pre-intervention with post-intervention outcomes and an assumption that costs for diabetic patients would have increased at the same rate as costs for nondiabetic patients were it not for the disease management program.9 In 1999, Domurat compared screening rates (e.g., hemoglobin A1c, urinary protein, serum lipids) and hospital utilization measures for enrollees in a diabetes care program that served the highest-severity (top 30%) diabetic patients versus lower-severity patients (the remaining 70%). Biomarker screening rates were higher for the higher-severity (care management) group than the lower-severity (usual care) group (e.g., rates of A1c testing of 84% for care management vs. 51% for usual care, \(P < 0.001\); rates of serum lipid testing of 75% for care management vs. 49% for usual care, \(P < 0.001\)), and inpatient utilization for the care management group decreased from baseline in 1995 (mean [SD] days 1.28 [5.93]) to 1997 (0.63 [2.24]). Although Domurat’s findings were likely attributable to regression to the mean and selection bias (i.e., testing rates would typically be higher for higher-severity than lower-severity patients), he concluded that the program “appears to reduce the number of hospitalizations and improve screening rates.”10

Disease management programs have achieved modest successes in trials with control groups. For example, Warsi et al.’s 2004 meta-analytic review and methodological critique of the literature on self-management education programs found “small to moderate” effects on intermediate end points, including biomarkers A1c and systolic blood pressure, for patients with diabetes and hypertension.11

Studies of patients with very high-severity conditions have also produced some success in modifying end point outcomes.12,13 For example, Rich et al. studied the use of nurse-directed multidisciplinary intervention, including education of patient and family, social service involvement, medication and “intensive” follow-up, in hospitalized patients aged 70 years or older and at high risk for readmission for CHF. Rates of readmission for CHF were 56.2% lower in the treatment group than in the control group (16.9% vs. 38.6%, respectively, \(P < 0.04\)). Improvements in quality-of-life measures and a reduction of $133 per patient per month were noted as well. However, reports of successful interventions based on studies with strong designs have tended to be the exception rather than the rule.14,15 and Warsi et al. observed that even among studies with control groups, methods used in assessing disease management programs varied widely and were generally “suboptimal.”11

As with so many health care innovations that seem to make sense to everyone at the time they are developed, the weakness in the research evidence supporting disease management did not hamper its enthusiastic adoption; the disease management industry’s annual revenues increased from $85 million to more than $600 million between 1997 and 2002.6 How the disease management industry will respond to the MHS setback is unclear. The MHS findings suggest that effective targeting of future disease management programs to beneficiaries most likely to benefit from them will continue to be challenging. Medicare beneficiaries in the MHS were randomized to equivalent intervention and control groups, but among those assigned to the intervention arm, those who actually agreed to participate in the program represented “a healthier subset of the intervention group.”3

In a separate Milliman report in mid-2008, Fitch and Pyenson provided additional perspective to investments in disease management and wellness programs by pointing out that “many wellness programs appear to be experiments on employees” rather than interventions with measurable outcomes.16 Second, since wellness programs target primarily persons without illness, medical claims are not helpful in measuring cost outcomes (e.g., about 11% of health plan beneficiaries will have no medical claims in a given year) or identifying potential candidates. Third, health risk assessment (HRA) questionnaires that measure health status may be useful in identifying a subset of the population that may benefit from wellness programs, but there are at least 3 factors that mitigate the utility of using HRAs to measure wellness: (a) significant incentives will be necessary to achieve a significant response rate, particularly among dependents, (b) self-reported data will likely be of lower quality since there are typically no audits or rules for ensuring data quality, and (c) self-selection bias is inevitable in HRA response and wellness program participation (i.e., people who participate in wellness programs will tend to be more motivated); so nonparticipants in wellness programs will...
not constitute a good control group for evaluation of a wellness program.

Fitch and Pyenson’s observations are consistent with a problem identified by the MHS program evaluators as a key factor in the program’s failure to meet savings goals: “the [disease management vendors] may have substantially overestimated the impact of their intervention on their ability to reduce the stream of beneficiary utilization.”

Because the ratio of nondisease-related to disease-related inpatient admissions was about 3:1, the evaluators pointed out, “unless the [disease management] programs are able to target and prevent hospitalizations for causes other than [CHF] and diabetes, projected cost savings related to reduced hospitalizations are unlikely to materialize.”

**A1c and Cholesterol Biomarkers Pale Under a Bright Spotlight**

In a clinical trial with a particularly appropriate acronym, the ILLUMINATE (Investigation of Lipid Level Management to Understand its Impact in Atherosclerotic Events) trial results released in late 2007 shook our confidence in the value of serum cholesterol levels in predicting clinical end points and made clear why the manufacturer had stopped the ILLUMINATE trial in December 2006. The ILLUMINATE results included the finding that torcetrapib increased the risk of morbidity and mortality despite raising high-density lipoprotein cholesterol (HDL-C) and lowering low-density lipoprotein cholesterol (LDL-C). Compared with baseline values, 12 months of treatment with torcetrapib (a cholesteryl ester transfer protein [CETP] inhibitor) + atorvastatin in 7,534 patients at high cardiovascular risk, was associated with a mean 72.1% increase in HDL-C and a mean 24.9% decrease in LDL-C (P<0.001 for both comparisons). However, these favorable changes in serum cholesterol biomarkers were associated with an increased risk of cardiovascular events (hazard ratio [HR]=1.25, 95% confidence interval [CI]=1.09-1.44, P=0.001) and all-cause death (HR=1.58, 95% CI=1.14-2.19, P=0.006).

The second major blow to our confidence in cholesterol biomarkers came less than 5 months later when the results of the Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression (ENHANCE) trial were released in the first week of April 2008, although our attention was piqued in December 2007 with the release of a Wall Street Journal investigation into the likely reasons for sandbagging the release of the ENHANCE trial results and a proposal by the drug study sponsors to change the definition of the primary end point in ENHANCE at the conclusion of the trial. After 24 months of treatment, mean (SD) LDL-C levels were 141.3 (52.6) mg per dL in the ezetimibe + simvastatin group and 192.7 (60.3) mg per dL in the simvastatin-only group (P<0.01). Yet, among patients treated with ezetimibe + simvastatin, the mean intima-media thickness (IMT) for 6 carotid artery segments increased by 0.0111 ± 0.0038 mm, trending more than (as editors, we hear this too often despite the absence of statistical significance and simply could not bring ourselves to delete this point) the mean increase of 0.0058 ± 0.0037 mm in the simvastatin-only group (P=0.29).

Similarly, the mean increase in the IMT of carotid and femoral arteries in the simvastatin + ezetimibe group (0.0182 ± 0.008 mm) and the simvastatin-only group (0.0033 ± 0.0079 mm) did not significantly differ (P=0.15). Not many clinical trial results rise to this level of significance in challenging conventional wisdom, and the fact that greater reduction in LDL was not associated with reduction in the rate of thickening of the walls of carotid arteries was startling.

Brown and Taylor summarized the practical clinical results of the ENHANCE study in a commentary, which was consistent with the statement from the American College of Cardiology in January 2008: “First, achieve targets for levels of LDL and HDL cholesterol (or of the ratio of total cholesterol to HDL cholesterol) with the use of statins plus drugs that have shown clinical benefits when added to statins (e.g., nicotinic acid, fibrates, and bile acid sequestrants), as tolerated. Second, use ezetimibe in patients who, despite the above-mentioned therapy, do not achieve their individual targets.” Brown and Taylor also compared the results of ENHANCE with ASAP (Atorvastatin vs. Simvastatin on Atherosclerosis Progression) conducted 6 years earlier: at 2 years, the increase in mean coronary artery IMT was 0.0058 mm for 80 mg simvastatin in ENHANCE versus 0.036 mm for 40 mg simvastatin monotherapy in ASAP (and -0.031 mm in the ASAP 80 mg atorvastatin group). While the 2 studies enrolled similar patients and used “nearly identical methods for measuring carotid-artery” IMT, the baseline IMT was 0.695 mm in the ENHANCE study versus 0.925 mm in ASAP. In commenting on ENHANCE, New England Journal of Medicine editors emphasized the paradox in the absence of difference in the mean IMT measures between the 2 groups despite 27% lower mean LDL-C and lower C-reactive protein levels among those treated with combination simvastatin-ezetimibe therapy. The editors agreed with Brown and Taylor that ezetimibe should be “reserved for patients who cannot tolerate these agents” (niacin, fibrates, and resins) as add-on therapy when “diet, exercise, and a statin have failed to achieve the target.”

Finally, the distinct absence of consensus about the value of simply lowering LDL-C as a means to improve population health was evidenced by reaction to the recommendation of the American Pediatrics Association released in July 2008 for the use of statins in some children in an attempt to reduce heart attacks later in life. The recommendation was met immediately by “furious debate,” including criticism such as that from a pediatric cardiologist, who observed that there are no data to support the use of statins for this purpose in this population.

**ACCORD and ADVANCE Question the Value of the Biomarker A1c in Lower-Is-Better Strategy for Type 2 Diabetes**

In what may seem like a conspiracy against accepted biomarkers, the results from 2 large clinical trials recently shook confidence...
in the importance of A1c in predicting end point outcomes, after being used for more than 30 years to measure the degree of control of glucose metabolism. The surprising results of these 2 clinical trials became available at a time when our memory was still vivid of the threat to the lower-is-better mantra for LDL-C cholesterol and higher-is-better mantra for HDL-C.

On February 6, 2008, the National Heart, Lung, and Blood Institute of the National Institutes of Health (NIH) announced that it had for safety reasons stopped 18 months early the intensive-therapy treatment arm of a large, ongoing North American clinical trial that enrolled 10,251 participants with type 2 diabetes and high cardiovascular risk, defined as either a diagnosis of heart disease or 2 or more risk factors for heart disease.24 At 1 year in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, the median A1c levels were 6.4% in the intensive-therapy group (target A1c below 6.0%) versus 7.5% in the standard-therapy group (target A1c from 7.0% to 7.9%). The first surprising finding was that there was no difference between the 2 groups in the number of patients who experienced a primary end point (nonfatal myocardial infarction [MI], nonfatal stroke, or cardiovascular-related death); 352 in the intensive-therapy group versus 371 in the standard-therapy group (HR = 0.94 with intensive therapy, 95% CI = 0.84-1.06, P = 0.32), (b) death from cardiovascular causes (HR = 0.88 with intensive therapy, 95% CI = 0.74-1.04, P = 0.12), or (c) all-cause death (HR = 0.93 with intensive therapy, 95% CI = 0.83-1.06, P = 0.28).

MTM Programs Designed to Reduce Biomarkers
Right in the middle of this renewed controversy about the value of the biomarkers in predicting clinical end points lands the current article by Stockl et al. in this issue of JMCP.23 Stockl et al. studied the effect of a Medicare Part D medication therapy management program (MTMP) intervention whose objective was to promote initiation of statin therapy in members with diabetes or CAD by sending educational materials and patient-specific information to physicians. Statin initiation rates were 12.1% in the intervention group and 7.3% in a comparison group (P = 0.001); the comparison group consisted of members who met all intervention group criteria except for the MTMP requirement that they be diagnosed with at least 3 of 5 chronic diagnoses of interest. The timing is perfect. Now, an even larger leap of faith is required to believe that Medicare beneficiaries with high medical care utilization and costs will experience end point clinical benefit from an intervention in which patients are encouraged to add statin therapy to reduce LDL-C, among a host of likely risk factors. The leap of faith is larger when one considers that (a) the intervention described by Stockl et al. was not guided by actual LDL-C laboratory values, and (b) these patients are already incurring at least $4,000 in annual pharmacy expenditures for Medicare Part D-covered medications.

ADVANCE—Clearly Negative Results for the Reduction of A1c and Prevention of Macrovascular Events
Following shortly on the heels of the termination by NIH of the intensive-therapy strategy in the ACCORD trial, the results of the Action in Diabetes and Vascular Disease: Preterax and Diamicron
us the results of one of the interventions apparently expected of managed care organizations in managing the costs and utilization of high-cost Medicare Part D beneficiaries via MTMP. Whether there is gold at the end of this rainbow will not be known for years although the disappointing results of the MHS demonstration suggest otherwise. In the meantime, we know that there are administrative costs involved in performing the intervention (estimated at $1.51 per physician intervention by Stockl et al.) and an annual statin cost of $275 per patient ($23 per month); Stockl et al. did not assess the additional costs of physician visits or laboratory tests associated with new statin therapy.

The calculation of return on investment set forth by Stockl et al. also becomes much different under a couple of revised assumptions. First, drug cost must be multiplied by a factor of about 4 if brand statin drugs are used instead of generic simvastatin, increasing direct costs for both the health plan and out-of-pocket costs for Medicare beneficiaries. Second, Stockl et al. used the results of the Scandinavian Simvastatin Survival Study (4S) to derive the number needed to treat (NNT = 11) with statin drug therapy for 6 years to prevent 1 major coronary event. Alternately, the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER) trial, which randomized 5,804 elderly patients (aged 70–82 years) with either a history of or risk factors for cardiovascular disease to either placebo or pravastatin 40 mg per day, demonstrated a 19% reduction in the risk of nonfatal MI and coronary death with pravastatin treatment, and the absolute rates of the primary end point after a mean of 3.2 years of treatment were 16.2% in the placebo group and 14.1% in the pravastatin group, yielding an NNT of 48. Substituting the 4S results with the PROSPER results in the model used by Stockl et al. increases direct drug cost to prevent 1 major coronary event from $16,335 to $42,240, easily overwhelming the estimated $28,990 the direct drug cost to prevent 1 major coronary event from the PROSPER results in the model used by Stockl et al. increases direct drug cost to prevent 1 major coronary event from the PROSPER results in the model used by Stockl et al.

Lower A1c Versus Cardiovascular Risk

Also in this issue of JMCP and in the middle of attempts to determine the implications of ACCORD and ADVANCE, the article by Starner et al. lays out nicely for us the 5 safety warnings that occurred in 2007 for 2 thiazolidinediones, pioglitazone, and rosiglitazone, and the opportunity that still exists for weighing benefit and harm in patients with type 2 diabetes who are treated with these drugs. In this post-marketing surveillance report, the authors found a 68% drop in rosiglitazone utilization from its peak of 99.1 claims per day per million members in February 2007, to 31.8 claims per day per million members in May 2008. However, there were still about 1 in 5 rosiglitazone patients at risk of a major cardiovascular event 1 year after 2 meta-analyses found an increased risk of MI in patients who had taken rosiglitazone and the release of a U.S. Food and Drug Administration (FDA) safety alert on May 21, 2007, regarding the increase of MI associated with rosiglitazone. There were also about 1 in 50 users of pioglitazone in May 2008 who had evidence of heart failure, but this incidence was down from 1 in 36 users in May 2007, 3 months before the black-box warning for exacerbation and precipitation of heart failure was added to the labels of pioglitazone and rosiglitazone.

Deeper investigation of the ACCORD trial shows that rosiglitazone was used in 90% of the intensive-therapy group versus 58% in the standard-therapy group, but the ACCORD trial investigators concluded that there was no link between rosiglitazone use and the increased rates of death in the intensive-therapy group. Dluhy and McMahon opined in an editorial published with the ACCORD trial in June 2008 that these results do not vindicate rosiglitazone from the findings of the meta-analysis of Nissen and Wolski in which rosiglitazone was associated with increased risk of MI and nearly significant increased risk of cardiovascular death. These editors also concluded that the 3.5-kg mean weight gain in the intensive-therapy group was explained by the use of thiazolidinediones and insulin in this group.

The observations of Dluhy and McMahon take us to a new awareness that glucose lowering alone does not predict a reduction in macrovascular events in patients with type 2 diabetes, at least in the first few years of treatment, when the results of ADVANCE, ACCORD, and the United Kingdom Prospective Diabetes Study (UKPDS) trials are considered together; for UKPDS, a reduction in cardiovascular events was not observed in patients with type 2 diabetes whose A1c was reduced from 8% to 7%. Therefore, it is logical that nonglycemic factors such as hypertension, dyslipidemia, and hypercoagulability may have an additive effect in patients with type 2 diabetes, and “before new targets are defined, it is worth reflecting that the currently established targets for hyperglycemia, hypertension, and hyperlipidemia are achieved” in less than 10% of patients. On the other hand, Dluhy and McMahon also raised a question about possible miscategorization of some of the excess deaths in ACCORD attributed to “unexpected or presumed cardiovascular disease” as alternatively attributable to hypoglycemia.

FDA Requests More Than A1c Lowering for Drug Approvals for Diabetes

The significance of the unexpected results of ACCORD and ADVANCE were not lost on the FDA, which called a meeting of its Endocrinologic and Metabolic Drugs Advisory Committee on July 1-2, 2008. Invited speakers included Steven Nissen, MD, talking about the need for cardiovascular assessment prior to FDA approval of antidiabetic drugs, and attendees included Clifford Rosen, MD, who is critical of newer antidiabetic drugs on the market that have not shown therapeutic advances over existing drugs. The FDA’s background memorandum ahead of the meeting of the Endocrinologic and Metabolic Drugs
Advisory Committee included the conclusion that “reduced risk of macrovascular complications in type 2 diabetes has not yet been established for any of the current available antidiabetic medications, including insulin.” At the meeting, Dr. Nissen proposed that the FDA impose a higher standard for approval of antidiabetic drugs, that new drugs must show no increased risk of cardiovascular disease. The FDA panel voted 14 to 2 on July 2, 2008, to require all new diabetes drugs to show no increased risk of cardiovascular harm.

**The Future of Biomarkers A1c and LDL-C and Risk Factor Management**

The sometimes disappointing results of rigorous tests of programs intended to increase adherence to guideline-based therapies and goals, including attainment of biomarker measures, may in part reflect limitations of the guidelines themselves. A 1999 evaluation of 279 guideline documents published between 1985 and 1997 found that the mean rate of adherence to methodological standards for identification and summary of evidence was only 33.6%; only 16.8% of guideline documents specified the method for identifying scientific evidence, only 14.3% specified the time period covered by the evidence review, only 60.2% quantified benefits and harms associated with treatment options, and a shockingly low 12.9% graded recommendations according to the strength of the evidence. The tenuous relationship of biomarkers such as A1c or LDL-C and cardiovascular events or death has been recognized in guidelines for the conduct of research in cost-effectiveness analysis. Three years ago, a task force on good research practices recommended against the use of intermediate end points such as the degree of LDL-C reduction when assessing cost-effectiveness.

Starfield et al. put the recently discovered lack of value of biomarkers, such as A1c and serum cholesterol, into broader perspective: over the last 3 decades, disease prevention has become risk factor management. The evolution in this thinking can be traced back to 1978, when prevention of disease (primary prevention) expanded to include interventions for the early detection and treatment of disease (secondary prevention), and later to the emergence of interventions “to improve function” for “those with severe cardiovascular dysfunction,” and with the definition from public health advocates, which essentially focuses on learning from our mistakes (interventions) in quality assurance and quality improvement.

There is presently a confluence of events that create an important opportunity to step back and survey the evidence for benefit versus risk in pursuit of disease prevention and disease management. At the least, conventional wisdom regarding the connection between biomarkers such as A1c and serum cholesterol and clinical end points has been exposed as not necessarily wise nor conventional. Conventional wisdom regarding the effectiveness of chronic care management in improving end point outcomes is being challenged as well and will require substantial rethinking and the gathering of high-quality evidence about the populations in which interventions are most likely to be effective. Now is also the time to reassess the transition that has occurred over the last 2 decades from disease management to pre-disease interventions based on blood pressure, serum cholesterol, and blood sugar. Current thresholds for these 3 biomarkers place 97% of all U.S. adults aged 50 years or older “at risk” by 1 or more of these biomarkers, but “only 8% of cardiovascular disease will occur in individuals with any combination of them.”

There is also the often overlooked fact that risk factors are not independent. Following the evidence is certainly leading us to some unexpected findings and reminding us that preventing specific diseases and chasing pre-disease markers are not the same as promoting health.

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REFERENCES


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