

Implications of recent clinical trials on pay-for-performance

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The use of pay-for-performance in medicine has grown rapidly over the past decade. According to a 2006 report, more than half of commercial health maintenance organizations in the United States use pay-for-performance in their contracts, and, in some cases, performance bonuses for physicians and hospitals are substantial.¹ In Great Britain, where pay-for-performance was formally introduced into the National Health Service in 2004, the salary of the average general practitioner increased the first year by \$40,000 and by another 10% the second year.^{2,3} Public insurance programs in the United States (e.g., Medicare, Medicaid, Veterans Health Administration) are also increasingly participating in pay-for-performance, with programs such as the Medicare Physician Quality Reporting Initiative and the Hospital Quality Alliance.⁴ While the data demonstrating how well pay-for-performance programs work are limited, there is growing consensus that financial incentives

in general, and pay-for-performance specifically, have a significant role to play in the improvement of health care quality in the United States.⁵⁻⁷

Pay-for-performance is focused on the management of chronic diseases, such as hyperlipidemia, diabetes, and hypertension. In the United States, over 900,000 people die from cardiovascular disease and diabetes each year, and chronic diseases, including cancer, account for over 75% of medical care costs and affect over 130 million people each year.⁸ Unfortunately, many patients with these conditions are undertreated and do not achieve their therapeutic goals, such as target blood pressure or lipid levels. For example, only 37% of people with hypertension have their blood pressure controlled and only 65% of hypertensive patients are being treated.⁹ Therefore, creating incentives to better control chronic diseases makes conceptual sense.

Ideally pay-for-performance in chronic diseases would be based on outcomes that really matter to pa-

tients, such as death, morbidity, and disability. Instead, many of the quality metrics used in pay-for-performance address process measures (e.g., the percentage of diabetic patients who receive glycosylated hemoglobin [HbA_{1c}] testing or a lipid profile each year). The few measures that attempt to address clinical outcomes actually measure surrogate markers like HbA_{1c}, low-density-lipoprotein (LDL) cholesterol, and blood pressure (Table 1).¹⁰

Given this information, what if evidence emerged that reaching a lower LDL cholesterol level, blood pressure, or HbA_{1c} did not always lead to better outcomes?¹¹ If morbidity and mortality are the true targets of pay-for-performance, and if pay-for-performance is to be a major part of the solution to the current health care problem, then we should be sure that the outcome measures we use are accurate surrogates and that the incentives we create are the right ones. Several recently published and high-profile studies questioned these assumptions and raised concerns about the appropriateness of current pay-for-performance measures.

Recent studies and questions about the use of surrogate markers. LDL cholesterol has long been accepted as a surrogate marker for coronary artery disease (CAD) mortality and is a widely used quality measure. Epidemiologic data show that people with high cholesterol have a higher incidence of CAD, and some clinical trials have found that lowering LDL cholesterol was associated with significant reductions in cardiovascular mortality.^{12,13} However, results of the recently published Ezetimibe and Simvastatin in Hyper-

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Table 1.

Rationale and New Evidence for Pay-for-Performance Measures in the United States^{10,a}

Condition	Pay-for-Performance Measure	Rationale for Measure	Evidence Questioning Measure	Potential Revisions to Measure
Hypercholesterolemia in patients with cardiovascular conditions	% patients who have a documented LDL cholesterol concentration of <100 mg/dL	Reducing cholesterol in patients with heart disease can reduce morbidity and mortality; guidelines set an LDL cholesterol target of <100 mg/dL	ENHANCE trial: simvastatin + ezetimibe lowered LDL cholesterol more than simvastatin alone (141 mg/dL vs. 193 mg/dL, respectively), but there was no change in carotid intima-media thickness	% patients who have documented LDL cholesterol level of <100 mg/dL; use of ezetimibe only acceptable when statins are contraindicated or goals not met on maximum doses of statins plus other evidence-based therapies (e.g., niacin)
Hypertension	% patients who have a diagnosis of hypertension and whose BP is ≤140/90 mm Hg	High BP is common and is a significant risk factor for CVD and stroke	ONTARGET trial: ACEI + ARB lowered BP better than ramipril alone (by 2–3 mm Hg) but had no incremental effect on mortality	% patients who have a diagnosis of hypertension and whose BP is ≤140/90 mm Hg while not on ACEI + ARB, except for patients with HF
Diabetes	% patients whose most recent HbA _{1c} is <7.0% (good control)	Diabetes is a leading cause of death and disability; lowering HbA _{1c} to 7% has been shown to reduce microvascular complications of diabetes	ACCORD trial: intensive lowering of HbA _{1c} to 6.4% was associated with increased mortality vs. usual care group with HbA _{1c} of 7.5% (HR, 1.22; <i>p</i> = 0.04)	% patients whose most recent HbA _{1c} was <7% but not <6% if on therapy, and not while on rosiglitazone

^aLDL = low-density lipoprotein, ENHANCE = Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression, BP = blood pressure, CVD = cardiovascular disease, ONTARGET = Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint, ACEI = angiotensin-converting-enzyme inhibitor, ARB = angiotensin II-receptor blocker, HF = heart failure, HbA_{1c} = glycosylated hemoglobin, ACCORD = Action to Control Cardiovascular Risk in Diabetes, HR = hazard ratio.

cholesterolemia Enhances Atherosclerosis Regression (ENHANCE) trial raise questions about using LDL cholesterol as a quality measure. ENHANCE evaluated whether adding a cholesterol-absorption inhibitor (ezetimibe) to maximum doses of the hydroxymethylglutaryl-coenzyme A reductase inhibitor simvastatin would slow the rate of atherosclerosis progression for patients with familial hypercholesterolemia.¹⁴ While patients randomized to receive ezetimibe plus simvastatin achieved significantly lower concentrations of LDL cholesterol than patients who received simvastatin alone (141 mg/dL versus 193 mg/dL), these lower

LDL cholesterol levels were not associated with reductions in atherosclerosis as assessed with the carotid intima-media thickness. There are many possible explanations for the study results, and a number of limitations exist with the use of the carotid intima-media thickness as a measure of coronary atherosclerosis and cardiac risk.¹⁵ Nevertheless, the ENHANCE trial results raise questions as to whether or not lowering LDL cholesterol levels alone is a specific enough measure of quality.

Another recent study raises similar questions about lowering blood pressure. Hypertension is an important risk factor for cardiovascular

disease and stroke, and the evidence is clear that lowering blood pressure reduces the risk of myocardial infarction and stroke.^{16,17} The Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint (ONTARGET) trial evaluated whether a regimen combining the renin-angiotensin blockers telmisartan and ramipril for patients with vascular disease or high-risk diabetes resulted in greater improvements in cardiovascular outcomes than each agent alone.¹⁸ Patients receiving combination therapy had mean blood pressures that were 2–3 mm Hg lower than patients treated with ramipril alone. Although this magnitude of

blood-pressure lowering should, according to the authors, have been associated with a 4–5% reduction in the rate of cardiovascular events, the rates of the study's primary efficacy outcome were no different among the combination therapy, ramipril, and telmisartan groups (16.3% versus 16.5% versus 16.7%, respectively).¹⁸ In addition, adverse events and poor renal outcomes were more frequent with combination therapy.^{18,19}

Several recent diabetes studies also raise similar concerns about the adequacy of HbA_{1c} as a surrogate marker. The National Heart, Lung, and Blood Institute sponsored the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, which compared intensive glucose lowering with a goal HbA_{1c} of <6.0% to less-intensive glucose control with an HbA_{1c} goal of 7.0% for diabetic patients at high risk of cardiovascular outcomes.²⁰ The trial was suspended in early 2008 because of the higher risk of death observed in the intensive glucose group, which is contrary to the conventional belief that patients with diabetes should achieve an HbA_{1c} that is as low as safely possible.²¹ Two other clinical trials that included patients with diabetes—the Veterans Affairs Diabetes Trial (VADT) and the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial—found no mortality benefit or reduction in cardiovascular events with intensive glucose control and lower HbA_{1c}.^{22,23} In addition, several highly publicized meta-analyses of the adverse cardiovascular outcomes associated with rosiglitazone questioned the potentially simplistic goal of merely achieving a low HbA_{1c} level.^{24,25}

Implications of these trials for pay-for-performance. Few would argue that cholesterol, blood pressure, and HbA_{1c} control are not important targets of therapy and care in a modern, quality-focused, health care

system. But these studies add to questions about how closely these proliferating quality measures really track the true quality of care and whether they will lead to improved endpoint outcomes.^{12,26–28} If the recent failure of the Medicare Health Support's disease-management demonstration project is an example of the danger of overreliance on intermediate measures, in combination with weak research evidence, then pay-for-performance is in similar trouble.^{11,29}

Physicians and practices are creating systems to collect data on the percentages of their patients who have reached targeted LDL cholesterol, HbA_{1c}, or blood pressure levels, and considerable time, energy, and money are being invested for this endeavor.^{30,31} Just as patients in the United States rely on the Food and Drug Administration (FDA) to make sure their medications are safe and effective for use, providers should rely on the Centers for Medicare and Medicaid Services, National Committee for Quality Assurance, and other organizations to be sure that quality measures are safe and effective before more resources are poured into pay-for-performance. The considerable criticism directed toward FDA because of the lack of resources needed to evaluate drug safety after the approval process portends a similar issue with continual reevaluation of pay-for-performance quality measures.

Lessons learned. Several lessons can be learned from these clinical trial results that may help as the United States and other countries continue to elevate pay-for-performance as a solution for rising health care costs.

These trials demonstrate that it is not only important *whether* quality goals are met but also *how* they are met. For example, the ENHANCE trial results suggest that the lower LDL cholesterol achieved by ezetimibe, which was approved by FDA for marketing on the basis of its ability to lower LDL cholesterol, may not

have the same effect on atherosclerosis and clinical events that statins have been widely demonstrated to have. There may be other mechanisms by which statins exert their effect, such as through C-reactive protein,³² which underscores the importance of valuing how as well as if these clinical targets are achieved. Similarly, the ONTARGET trial results and the recent meta-analyses of rosiglitazone suggest that, not only should incentives be created to achieve specific blood pressure and HbA_{1c} levels, the best ways to reach those targets should be established. Outlining specific care pathways or evidence-based medication use as part of these clinical targets may be a way to improve these performance measures (Table 1). Pay-for-performance could be based on entire pathways of care—from diagnosis to management to disposition—rather than based solely on specific therapies or laboratory results.

The clinical trials underscore the need for flexible incentives that can respond to new information and efficiently incorporate new evidence. A health care system that needs to improve quality quickly will often need to use surrogate measures to make informed decisions about clinical targets when true outcome data are not available. However, the time pressures cannot absolve the system from putting in place a robust mechanism for updating (and potentially suspending) these quality measures in the face of new evidence (e.g., Phase IV trials in drug development). Should hospitals, insurers, and providers continue to be paid based solely on whether they achieve these surrogate targets? It could be argued that it is poor quality care to have lowered a diabetic patient's LDL cholesterol to <100 mg/dL using ezetimibe if the option exists to use a statin, considering the evidence presented above.

Similarly, is the last blood pressure measurement for a patient with

hypertension of <140/90 mm Hg a good surrogate marker for quality care if the patient is on combined angiotensin-converting-enzyme inhibitor and angiotensin II-receptor-blocker therapy when the option exists to control blood pressure using one drug or the other? Perhaps pay-for-performance contracts should have a mechanism in place to update the performance measures midyear, in addition to routine annual review, if data emerge that question the validity of the performance measure (and the organizing bodies in quality measurement agree) and the risks to patients or to the health system are too great to continue through the contract.

We do not aim to question the concept of pay-for-performance, which is intuitively sound, or to question the validity of all intermediate outcomes. We do, however, question the selection of these particular measures as they are currently structured and emphasize the need to update them when new evidence emerges. What then should we do for LDL cholesterol, blood pressure, and HbA_{1c} in the meantime? Perhaps we should drop these measures, and any other questionable measures, entirely from pay-for-performance while waiting for clarifying data. This probably is the wrong solution, knowing that evidence is always evolving. More reasonably, we should aim to make these important measures more specific, open to revision, and responsive to new evidence (Table 1). These tasks are difficult to accomplish considering the mutable nature of evidence and the nearly impossible task of formally outlining every specific strategy for achieving surrogate targets. The solution, however, is not to simply ignore the problem and move on. When it comes to quality, stubbornly focusing on the wrong surrogate measures of true performance will lead us, and our patients, in the wrong direction.

References

- Rosenthal MB, Landon BE, Normand SL et al. Pay for performance in commercial HMOs. *N Engl J Med.* 2006; 355:1895-902.
- Doran T, Fullwood C, Gravelle H et al. Pay-for-performance programs in family practices in the United Kingdom. *N Engl J Med.* 2006; 355:375-84.
- BBC News. GP pay £110,000 after a 10% rise. <http://news.bbc.co.uk/2/hi/health/7070655.stm> (accessed 2008 May 5).
- Jha AK, Li Z, Orav EJ et al. Care in U.S. hospitals—the Hospital Quality Alliance program. *N Engl J Med.* 2005; 353:265-74.
- Epstein AM. Pay for performance at the tipping point. *N Engl J Med.* 2007; 356:515-7.
- Petersen LA, Woodard LD, Urech T et al. Does pay-for-performance improve the quality of health care? *Ann Intern Med.* 2006; 145:265-72.
- Rosenthal MB, Frank RG. What is the empirical basis for paying for quality in health care? *Med Care Res Rev.* 2006; 63:135-57.
- Centers for Disease Control and Prevention. Chronic disease prevention and health promotion. Chronic disease overview. www.cdc.gov/nccdphp/overview.htm (accessed 2008 May 21).
- Ong KL, Cheung BM, Man YB et al. Prevalence, awareness, treatment, and control of hypertension among United States adults 1999-2004. *Hypertension.* 2007; 49:69-75.
- National Committee for Quality Assurance. 2008 HEDIS performance measures. www.ncca.org/tabid/697/default.aspx (accessed 2009 Feb 6).
- Curtiss FR, Fairman KA. Looking for the outcomes we love in all the wrong places: the questionable value of biomarkers and investments in chronic care disease management interventions. *J Manag Care Pharm.* 2008; 14:563-70.
- Psaty BM, Lumley T. Surrogate end points and FDA approval: a tale of 2 lipid-altering drugs. *JAMA.* 2008; 299:1474-6.
- Rader D, Hobbs H. Disorders of lipoprotein metabolism. In: Fauci A, Braunwald E, Kasper D et al., eds. Harrison's principles of internal medicine. Vol 17. Columbus, OH: McGraw-Hill; 2008:2426.
- Kastelein JJ, Akdim F, Stroes ES et al. Simvastatin with or without ezetimibe in familial hypercholesterolemia. *N Engl J Med.* 2008; 358:1431-43. [Erratum, *N Engl J Med.* 2008; 358:1977.]
- Brown BG, Taylor AJ. Does ENHANCE diminish confidence in lowering LDL or in ezetimibe? *N Engl J Med.* 2008; 358:1504-7.
- Neal B, MacMahon S, Chapman N. Effects of ACE inhibitors, calcium antagonists, and other blood-pressure-lowering drugs: results of prospectively designed overviews of randomised trials. Blood Pressure Lowering Treatment Trialists' Collaboration. *Lancet.* 2000; 356:1955-64.
- Ritz E. Total cardiovascular risk management. *Am J Cardiol.* 2007; 100:53J-60J.
- Yusuf S, Teo KK, Pogue J et al. Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med.* 2008; 358:1547-59.
- Mann JF, Schmieder RE, McQueen M et al. Renal outcomes with telmisartan, ramipril, or both, in people at high vascular risk (the ONTARGET study): a multicentre, randomised, double-blind, controlled trial. *Lancet.* 2008; 372:547-53.
- The Action to Control Cardiovascular Risk in Diabetes Study Group, Gerstein HC, Miller ME et al. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med.* 2008; 358:2545-59.
- National Institutes of Health. For safety, NHLBI changes intensive blood sugar treatment strategy in clinical trial of diabetes and cardiovascular disease. <http://public.nhlbi.nih.gov/newsroom/home/GetPressRelease.aspx?id=2551> (accessed 2008 May 10).
- Duckworth W, Abraira C, Moritz T et al. Glucose control and vascular complications in veterans with type 2 diabetes. *N Engl J Med.* 2009; 360:129-39.
- The ADVANCE Collaborative Group, Patel A, MacMahon S et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med.* 2008; 358:2560-72.
- Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *N Engl J Med.* 2007; 356:2457-71. [Erratum, *N Engl J Med.* 2007; 357:100.]
- Singh S, Loke YK, Furberg CD. Long-term risk of cardiovascular events with rosiglitazone: a meta-analysis. *JAMA.* 2007; 298:1189-95.
- Heath I, Hippisley-Cox J, Smeeth L. Measuring performance and missing the point? *BMJ.* 2007; 335:1075-6.
- Wodchis WP, Ross JS, Detsky AS. Is P4P really FFS? *JAMA.* 2007; 298:1797-9.
- McMahon LF Jr, Hofer TP, Hayward RA. Physician-level P4P—DOA? Can quality-based payment be resuscitated? *Am J Manag Care.* 2007; 13:233-6.
- Abelson R. Medicare finds how hard it is to save money. *N Y Times.* www.nytimes.com/2008/04/07/business/07medicare.html?_r=1 (accessed 2009 Feb 4).
- Hillestad R, Bigelow J, Bower A et al. Can electronic medical record systems transform health care? Potential health benefits, savings, and costs. *Health Aff (Millwood).* 2005; 24:1103-17.
- Miller RH, Sim I. Physicians' use of electronic medical records: barriers and solutions. *Health Aff (Millwood).* 2004; 23:116-26.
- Ridker PM, Danielson E, Fonseca FA et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med.* 2008; 359:2195-207.