EDITORIAL

The Future of Prescription Drug Cost-Sharing: Real Progress or Dropped Opportunity?

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It was October 25, 1986. Game 6 of the World Series between the New York Mets and the Boston Red Sox was tied in the bottom of the 10th inning, with 2 outs and 1 runner on base. The Mets' Mookie Wilson hit a routine grounder in the direction of first baseman Bill Buckner, who bent down to scoop it up. But in one of the most infamous incidents in sports history, the ball sailed past Buckner's outstretched glove and rolled through his legs into right field. The Mets scored, won the ball game, and eventually took the Series title. The Sox did not make another trip to the World Series until 2004. Their critical moment of opportunity had been lost.[1]

Managed care pharmacy currently faces a critical moment of opportunity as it considers the future of cost-sharing for prescription drugs. Nearly every serious observer of health care outcomes research understands that decisions about patient out-of-pocket (OOP) cost should be based on evidence. But what is less universally recognized is the importance of catching the *right* evidence to avoid dropping the ball in today's cost-sharing game.

The key to understanding our industry's challenge (and opportunity) lies in recognizing that a paradigm transition is underway in both business and academic sectors of health care policymaking. A once almost universally held view, that generic/brand cost-share differentials and increases in cost-sharing to keep pace with inflation are the best tools to align consumer behavior with desired clinical and economic outcomes, is gradually being challenged by a new model of patient incentives. According to this new model, reduction or elimination in cost-sharing for prescription drugs has the potential to cure ills ranging from patient noncompliance to rising costs for medical services.[2] As an industry, we can either respond to the paradigm shift to ensure that our bases are covered or risk dropping the ball.

An Early Paradigm: Increasing Out-of-Pocket Cost Without Adverse Consequences

The classic and best-designed study of the effects of cost-sharing, the RAND Health Insurance Experiment (HIE), randomized 2,750 families to receive medical care (1) free of charge, (2) at a 25%, 50%, or 95% coinsurance rate for all services, or (3) at a 95% coinsurance rate for outpatient services with free hospital inpatient care. Maximum annual OOP cost was indexed to family income, and all families received a lump sum payment equal to their worst-case OOP outlays to ensure that no family was financially harmed by participation in the experiment.[3,4]

HIE researchers found that as OOP cost increased, health care expense decreased. For example, annual total health care expenses in 1984 dollars were 45% higher for enrollees in the free-care plan ($749 per member per year [PMPY]) than for enrollees who were charged 95% coinsurance for all services ($518 PMPY) and 18% higher than for enrollees in the 25% coinsurance group ($634 PMPY).[3] Annual prescription drug expenses in 1983 dollars were 60% higher in the free plan ($54.41 PMPY) than in the 95% coinsurance plan ($33.95 PMPY).[5] The savings observed for the higher cost-sharing group were derived from lower utilization (e.g., number of physician visits and hospitalizations, number of prescriptions filled) rather than from reductions in cost per service. Notably, researchers posited that lower prescription drug expenditures were attributable to a smaller number of medical contacts (e.g., office visits) rather than to substitution of lower-cost for higher-cost medications, since neither cost per prescription nor generic fill rate was affected by cost-sharing.[5]

The decreased health care expense attributable to cost-sharing in the HIE study was not associated with negative health consequences. Although enrollees subjected to cost-sharing used fewer services, their health outcomes did not differ from those of enrollees who received free care.[3,4] The only exceptions were observed in the group of enrollees at or below the lowest 20th income percentile. For this low-income group, free care was associated with lower blood pressure among patients with hypertension, modestly better vision among patients with vision problems, and improvement in 2 measures of dental health.[3,4] Satisfaction with coverage was generally high and unaffected by the amount of cost-sharing, and enrollees in higher cost-sharing plans were less likely to worry about their health and had fewer restricted-activity days (including time spent in medical care) than those receiving free care.[4]

Because the HIE's findings supported the use of cost-sharing for most enrollees with the exception of low-income persons, the HIE's authors later speculated that their findings had encouraged an industry-wide move away from first-dollar health insurance coverage beginning in the early 1980s. If so, the HIE's authors argued, the investment of $80 million in research costs to conduct the HIE had yielded savings of $7 billion in reduced hospital expenditures from 1982 to 1984.[3]

The Early Cost-Sharing Paradigm Applied to Prescription Drugs

The Kaiser Family Foundation estimates that from 2000 to 2006, mean prescription drug copayments under U.S. employer-sponsored health plans increased from $7 to $11 (about a $0.67 average annual increase) for generics, from $13 to $24 (about a $1.83 average annual increase) for preferred brands, and from $17 to $38 (about a $3.50 average annual increase) for non-preferred

brands.[6] The largest average copayment increase occurred between 2001 and 2002, when the mean non-preferred brand copayment changed from $20 to $25. Increases in cost-sharing at point of sale had been advocated by proponents of managed competition, who argued that without sufficient financial responsibility for their preferences (e.g., for advertised brand-name medications instead of generic drugs, for richer versus more basic insurance benefits), consumers would have no "direct personal interest in economical medical care" and thus would not accept any cost consciousness in the health care system.[7,8] Yet the need to measure the *outcomes* of copayment increase was widely recognized; the prevailing concern was whether higher OOP cost outlays would prompt or even force patients to reduce use of essential medication.[9-11]

Consistent with the prevailing paradigm, most drug benefits research conducted since the mid-1980s has measured the impact of cost-sharing increase, usually applied to flat copayment amounts, on a variety of outcomes including utilization, cost, and medication adherence.[12-26] Several studies employing strong quasi-experimental (pre-post with comparison group) designs examined modest copayment increases (i.e., change amounts ranging from $5 to $13 for brand medications). These amounts are greater than the annual average changes from 2000 to 2006 as reported in the Kaiser Family Foundation data[6] but are typical of changes implemented in commercially insured populations at any single point in time.[9]

These quasi-experimental studies found that modest copayment increases produced savings, particularly to net payer cost after subtracting member cost-share amount, without affecting adherence to chronic medication therapy[12-15] or utilization of medical services, including hospitalizations, emergency room visits, and physician office visits.[13,15] Controlled assessments of formulary compliance have similarly found that modest increases in patient cost-sharing are associated with increased utilization of preferred brands or generics.[12,14,16,17]

Landsman et al.'s more recent quasi-experimental study of response to higher copayment change amounts (increases of up to $25 for non-preferred brand medications) in commercially insured populations assessed price elasticity, the ratio of change in quantity to change in price, which is a standard measure of price sensitivity.[18] Study findings demonstrated price *inelasticity* (i.e., insensitivity to price change) among recent users (2 or more pharmacy claims in the therapy class within the 3 months prior to the copayment change) of angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), calcium channel blockers (CCBs), and HMG-CoA reductase inhibitors (statins). Price elasticity was moderate for cyclo-oxygenase-2 inhibitors, nonsteroidal anti-inflammatory drugs, 5-hydroxytryptamine receptor agonists (triptans), and selective serotonin reuptake inhibitors (SSRIs).

In a separate analysis of the same study sample, the authors documented higher "discontinuation" rates for patients subject to copayment increases than for a comparison group in several drug classes, including ACEIs, ARBs, statins, SSRIs, and tricyclic antidepressants. However, in the "discontinuation" analysis, the authors included patients whose most recent use of the drug class was more than 3 months prior to the copayment change and defined switches from ARBs to ACEIs, or from ACEIs to ARBs, as discontinuations.[18] Thus, the price elasticity analysis was likely a better measure of response to price change than was the discontinuation analysis. Notably, in both analyses Landsman et al. excluded 20% of the potential sample of patients because of copayment discrepancy (i.e., at least 1 copayment actually paid by the patient did not match the copayment that should have been paid according to the benefit design), a decision that had the effect of removing from the sample all patients whose first prescription filled under the higher copayment system was "grandfathered" in (provided at the lower copay).[18] Because "grandfathering" is a commonly used mechanism to ease patients' transition into higher copayment designs, excluding the "grandfathered" patients likely biased Landsman et al.'s analyses in favor of finding higher discontinuation rates for the copayment change group.

One exception to the general rule of inelastic consumer response to a cost-sharing increase is the situation, more common in publicly funded coverage than in commercial insurance, in which members are enrolled in plans with atypical benefit designs (e.g., single-tier, very low or $0 copay) prior to the benefit design change.[14,19-21] Huskamp et al.'s quasi-experimental analysis of discontinuation rates in 3 classes of chronic medications (ACEIs, proton pump inhibitors [PPIs], and statins) showed that users of non-preferred brand drugs in a copayment intervention group, who experienced a $12 increase in the highest copayment tier at the community pharmacy (from a 2-copayment tier at $6/$12 [generic/brand] to a 3-copayment tier at $6/$12/$24 [generic/preferred brand/non-preferred brand]), did not discontinue therapy at greater rates than did non-preferred brand drug users in a comparison group, who experienced no copayment change to a $6/$12 (brand/generic) structure.[14] In fact, in that analysis, discontinuation rates for ACEIs were actually *lower* for the intervention group (8.3%) than for the comparison group (15.8%). However, non-preferred brand drug users who experienced a simultaneous $23 copayment increase and major tier-structure change (from a $7 single-copayment tier to an $8/$15/$30 3-copayment tier structure) discontinued therapy at higher rates than did non-preferred brand drug users who experienced no copayment change (16% vs. 6% for ACEIs, 21% vs. 11% for statins, and 32% vs. 19% for PPIs).[14]

As Curtiss pointed out in a January/February 2004 editorial critical of Huskamp et al.'s work, the finding of a higher discontinuation rate for the group experiencing a $23 copayment increase was suspect.[27] The comparison group in that analysis had a 2-tier $8/$15 (brand/generic) copayment design, not at all comparable with the intervention group's $7 single-tier copayment design in the pre-intervention period. Additionally,

because of the plan's formulary, the number of tier 3 statin users was extremely small, and the difference between the 21% (intervention) and 11% (comparison) statin discontinuation rates represented only 8 people. Nonetheless, Huskamp et al.'s results at least suggested the possibility that drastic copayment changes negatively affect adherence.

Roblin et al.'s study of oral hypoglycemic use in 5 managed care organizations produced a similar result using a time series with comparison group design.[26] Although cost-sharing increases of $1 to $10 were found to be unrelated to average daily dose of oral hypoglycemic drugs, increases of more than $10 were associated with a decline of 2.6% per month in average daily dose. However, less than 2% of the study sample experienced a copayment change of more than $10, and of that group 69% of patients had received their medication either free of charge or for a copayment of <$5 per month prior to the copayment change. Thus, only large and atypical increases in beneficiary cost-share, not smaller and much more typical increases, were associated with declines in utilization.

Even among those accustomed to free medication, the effects of introducing a cost-sharing increase do not appear to be uniform. Dormuth et al. and Schneeweiss et al. conducted several studies of elderly (aged ≥65 years) beneficiaries in British Columbia's public health care system, examining the effects of sequential changes.[19-21] Beneficiary cost-share changed first from free medication to a flat copayment of either $10 or $25, and then from the copayment design to 25% coinsurance with an income-based deductible. Results were inconsistent across therapeutic classes and disease states. Adherence (defined as percentage of days covered [PDC] >80%) to newly initiated statin therapy and use rates for inhaled steroids, inhaled anticholinergics, and inhaled beta-2 agonists were significantly lower under cost-sharing.[19,20] However, adherence to beta-blocker therapy was only marginally related to cost-sharing (difference of 0.8 to 1.3 percentage points),[21] and initiation rates for a beta-blocker[21] or a statin[20] following hospitalization for an acute myocardial infarction were unrelated to cost-sharing change.

Consistent with the RAND HIE's finding of increased vulnerability to cost-sharing among lower-income persons, additional exceptions to the general rule of consumer price insensitivity to prescription drug cost-sharing increases include low-income enrollees and patients with serious mental illness.[3,4,22-25] Tamblyn et al.'s study of low-income and elderly persons in Quebec found that a change from $0 to $2 copayments to 25% coinsurance with income-indexed OOP maximums was followed by reductions in essential drug use by 9% for the elderly and by 14% for low-income persons; however, that study lacked a comparison group.[22] A better-designed quasi-experimental study of veterans with schizophrenia, conducted by Zeber et al., found that patients subject to a $5 drug copayment increase (from $2 to $7) reduced use of psychotropic medications by nearly 25%; a slight increase in psychiatric admissions and total inpatient days occurred as well.[23] That study's patient population was particularly vulnerable to the effects of a cost-sharing increase since, as the authors pointed out, 95% of veterans with schizophrenia earn less than $26,000 per year.

Consumer-Driven Health Care: The Paradigm of Cost-Sharing Increase at Its Peak

Buoyed by research evidence that desired outcomes of cost-sharing change (generally inelastic consumer response, increased use of preferred brands and generics, overall cost savings) were being achieved in commercial populations, policy analysts began to speculate that asking consumers to pay a higher portion of total cost could be a potential, if partial, solution to the problem of balancing the sustainability of the health care insurance system against consumer preferences. Advocates of higher cost-sharing argued that members could freely choose among different options available (e.g., when selecting health care coverage or providers or requesting specific prescription drugs from their physicians) but should bear some financial responsibility for their choices.[28]

The higher cost-sharing paradigm appeared to reach its peak in market-based models, particularly in consumer-driven health care (CDHC), a financing approach that typically combines a high-deductible health plan with tax-advantaged accounts that can be used by enrollees to pay expenses for medical services and prescription drugs. Typical consumer-driven health plan (CDHP) features also include lower monthly premiums and greater consumer choice of services and providers, although these features are not universal.[28] As RAND Health researchers have pointed out, CDHPs' cost-sharing features are similar to the design used in the HIE's 95% coinsurance plan.[4] Among CDHC advocates, expectations for its potential to transform the health care delivery system are high. "Armed with money in hand and information they can act on, U.S. consumers can be an impatient and demanding bunch," one CDHC proponent wrote in 2005. "This is where the revolution really begins: in the impact such informed buyers will have on the rest of the health care system."[29] In this view, consumers' ready willingness to reject "goods and services that no longer meet their needs" will "impose a level of discipline and accountability on health care that has long been missing."[29]

Whether consumers have the ability to determine which services meet their needs is open to question. The HIE found that enrollees in higher cost-sharing arrangements reduced their use of effective and less effective medical care by approximately equal amounts.[4] However, a much more recent quasi-experimental (pre-post with comparison group) study suggested that CDHP enrollees distinguish between necessary and unnecessary services. That study found that in the 12 months following an insurance enrollment process in which beneficiaries were given no choice of plans, new enrollees of a high-deductible health plan (HDHP, n=8,724) were more likely than a comparison group of traditional insurance enrollees (n=59,557) to reduce use of *repeat* emergency department visits for conditions of low severity

(e.g., upper respiratory tract infections, neck and back pain, headache, nausea) and indeterminate severity (e.g., abdominal pain; open wounds of extremities, head, neck, and trunk; nonspecific chest pain; superficial injury). For low-severity conditions, repeat emergency department visit rates per 1,000 members for the 12-month baseline and follow-up periods, respectively, were 142.5 and 92.1 for the HDHP members versus 128.0 and 132.5 for the traditional insurance members. Notably, neither *initial* emergency department use nor visits for high-severity conditions were significantly related to HDHP enrollment.[30]

Despite questions about consumers' ability to make good health care choices, CDHP availability and enrollment have increased rapidly in the past few years. A recent nationwide survey of employer-sponsored health plans estimated that from 2005 to 2006, the percentage of large companies (20,000 or more employees) offering a CDHP increased from 22% to 37%. For smaller companies (10 to 499 employees), the percentage increased from 2% to 5%.[31]

Opposition to Cost-Sharing Increases: Support for a Paradigm Shift

In about 2003, opposition to higher cost-sharing began to emerge from 2 camps that can best be described as "strange bedfellows." In one camp, political advocates of universal health care coverage began arguing against market-based approaches to health care delivery, claiming that CDHC's high OOP requirements prompt patients to curtail or cease use of necessary and cost-effective medical services. One claim was made by Commonwealth Fund president Karen Davis on the *NewsHour with Jim Lehrer* in February 2006. When asked by *NewsHour* host Ray Suarez what effects Davis believed would result from widespread implementation of CDHC, she answered that the Commonwealth Fund had "supported a survey … about people who had these high-deductible plans with health savings accounts and they do report that they go without needed care, they don't fill a prescription where they really should be taking their prescription to control a chronic condition."[32] Davis argued that, ultimately, higher overall medical cost would result from lower adherence.

Davis did not mention that the response rate to the survey was only 6.5%,[33] that the degree to which its Web-based respondent pool represented insured persons in the United States was questionable, or that the CDHC-related medical care reductions were actually proportionally larger for *higher*-income than for lower-income enrollees.[34] Notably, compared with traditional insurance respondents to the Commonwealth Fund survey, CDHP-enrolled respondents reported similar medical utilization (e.g., office visit rates) and significantly better health; yet they indicated greater unmet health care needs.[34] The obvious methodological and logical weakness of this evidence was typical of early studies of high-deductible plans; an October 2006 review of early experience with CDHC noted that the "evidence needed to draw firm conclusions about CDHC's overall effects" was nonexistent.[35]

From another camp at about the same time (beginning in about 2002), numerous studies, many sponsored by pharmaceutical manufacturers, began documenting cross-sectional associations between higher prescription drug cost-sharing amounts and lower rates of medication utilization and adherence.[36-43] The change in research methodology from strong quasi-experimental designs to cross-sectional analyses was seminal. Cross-sectional analyses compare different groups at the same points in time. They do not directly assess response to a change or intervention; they simply document statistical associations (e.g., between cost-sharing category and outcomes) that might or might not be causal.[44,45]

A marked shift in the findings of cost-sharing research reflects the magnitude of the methodological change. An early cross-sectional study conducted by Joyce et al. of RAND Health investigated employer-based coverage provided through 25 large companies. Study authors used medical and pharmacy claims data to compare prescription drug expenditures under various benefit designs. Statistical modeling controlled for demographic characteristics, including age, gender, work status, and median household income in the enrollee's ZIP code; clinical characteristics, including comorbidities; and health plan characteristics, including cost-sharing for physician office visits. The model predicted that average PMPY prescription drug spending was $725 for a 1-tier plan with a $5 copayment, $678 for a 2-tier plan with $5/$10 copayments, $666 for a 3-tier plan with $5/$10/$15 copayments, and $436 for a 3-tier plan with $10/$20/$30 copayments.[38] Thus in sharp contrast to the very modest utilization effects documented in quasi-experimental work,[12,13,15] these cross-sectional results indicated that, for example, utilization was a dramatic 35% lower in a $10/$20/$30 benefit than in a $5/$10/$15 benefit.[38] Another study conducted by Taira et al., again using a cross-sectional methodology, found that compliance (medication possession ratio [MPR] >80%) with antihypertensive medication was 24% lower for medications with a $20 copayment compared with a $5 copayment.[39]

In discussions of the findings of this cross-sectional work, claims going far beyond the available data have been remarkably and unfortunately common. For example, Goldman et al. asserted that they had documented "significant price responsiveness" among health care consumers, even though their study's design had not actually measured price *change* at all (only an association between utilization measures and higher versus lower prices, supplemented by a mathematical *simulation* of how consumers behave when prices change).[37] Similarly, in reporting results of a study that included no measures of medical costs or utilization at all, Joyce et al. concluded that "pharmacy benefit managers and their sponsors may be designing prescription benefit packages that reduce the costs of pharmaceuticals but increase overall medical costs."[38] Although knowledgeable observers at the time pointed out the lack of methodological rigor in cross-sectional work compared with stronger quasi-experimental designs,[45,46]

the body of cross-sectional work remains influential and is often cited as a key factor underlying the new "lower-is-better" view of cost-sharing.[2,47,48]

The association between pharmaceutical manufacturer support (funding and/or personnel) and the results of cost-sharing research should not go unnoticed. Of pharma-supported studies of the relationship between patient outcomes and cost-sharing in commercially insured populations,[14,16-18,36,37,39,43] most have produced at least 1 major finding critical of cost-sharing.[14,18,36,37,39,43] In contrast, of studies that were not pharma-supported,[12,13,15,26,38,42] few have produced findings clearly critical of cost-sharing.[38,42] Notably, 2 quasi-experimental studies that produced findings critical of cost-sharing were pharma-supported,[14,18] and both employed study methodologies that were unusual or questionable. The use of unusual methodology in producing findings critical of cost-sharing was highlighted by Curtiss in 2004, when he pointed out that the headline press attention to the findings of the Huskamp et al. study[14] ignored important ambiguities in its methods and findings.[27] Curtiss reminded us that "like many things in life, the truth and wisdom" of cost-sharing research "are in the details."[27]

A New Paradigm for Cost-Sharing: Copayment Reductions to Improve Outcomes

Not surprisingly, given the change in the direction of research findings, a new paradigm that had first been mentioned in 2001 began to gain substantial traction beginning in about 2004.[41,42,47-52] Policy analysts began to describe associations between higher patient OOP cost and lower prescription drug utilization in a different way—this time emphasizing the association between *lower* OOP cost and higher utilization. Instead of asking how much patient OOP cost could be increased without *damaging* outcomes, policy analysts began asking how much OOP cost should be decreased to encourage adherence to prescription drug therapy and *improve* outcomes.[41,42,47,48]

For example, Ellis et al. in 2004 found an association between higher copayments and lower statin adherence rates and asked whether copayment levels should be targeted, with lower copayments for patients "with the most to gain" from statin therapy.[41] The authors argued that "coincidence alone cannot explain" why rates of discontinuation are lower in clinical trials ("where study medication is almost always provided free of charge to study subjects") than in routine clinical practice. The authors suggested that providing lower-cost or no-cost medications to patients in routine clinical practice would improve medication adherence.[41] Goldman et al.'s statistical simulation in 2006, based on cross-sectional analysis of medical and prescription claims data, produced a similar result. After finding associations between lower statin copayments and higher MPRs, and between higher MPRs and lower medical costs (but without actually measuring the relationship between prescription drug cost-sharing and medical costs), the authors concluded that "varying copayments for [cholesterol-lowering] therapy by therapeutic need would reduce hospitalizations and [emergency department] use."[42]

By 2007, the new concept that reducing OOP cost would yield big medical cost savings had taken hold in a small but growing share of the commercial insurance market. Large employers, including Procter & Gamble, Eastman Chemical, Pitney Bowes, and the Marriott Corporation, began reducing or eliminating copayments for chronic medications.[2,48,50] For Pitney Bowes, the copayment reductions were part of a larger strategy that included elimination of all deductibles and provision of free preventive care, enhanced wellness programs, access to free clinics and fitness centers, and healthier snacks in the company cafeteria.[47,49] Large insurers, including Humana, Aetna, and Cigna, began offering designs in which copayments were lowered or eliminated for medications that offer greater clinical benefits.[2,48]

A *Wall Street Journal* article announced in May 2007 that payers "desperate for ways to curb soaring health-care costs" could find relief in copayment reduction. The policy of "shifting costs onto workers and encouraging them to use lower-cost generics" was the subject of an "about-face," the article said, because "the new model" of copayment reduction for chronic illness "makes better medical sense."[48] Benefits designers began offering cost modeling tools to assist clients in offsetting copayment changes in different therapeutic classes (e.g., lowering copayments in essential medication classes but increasing copayments for less essential drugs).[52] Despite the typically long-term and progressive nature of chronic illness, proponents even began to hint that short-term savings could be achieved from copayment reduction, albeit without supporting evidence: "Employers worry about the cost of this design," commented one of its proponents, "[but] I tell them that reducing the costs of these drugs means their employees will be working instead of in a hospital."[2]

State of the Art: Cost-Sharing Research Today

Articles recently published in *JMCP* provide additional lessons in the strengths and weaknesses of cost-sharing research today. In the October 2007 issue of *JMCP*, Zhang et al. reported the results of a study of patients newly initiating therapy with a single-agent angiotensin system blocker.[53] Their analyses assessed the relationship between copayment for the first prescription fill and several measures of medication adherence during the first 6 months of treatment, statistically controlling for numerous variables representing predisposing factors (age, gender, previous use of antihypertensive medications other than angiotensin system blockers, and race measured at ZIP code level); enabling factors (urban vs. rural residence, whether pharmacy benefit included an OOP maximum, and several measures of medical and prescription drug utilization); and need factors (hypertension, cardiac conditions, diabetes, and dyslipidemia). The authors reported that every $1 of additional patient OOP cost for a 30-day supply of the initial prescription was associated with a 1.9% increase in total number of days without angiotensin

system blocker medication, a 2.8% increase in the odds of having a PDC <80%, and a 1.0% increase in the risk of having a treatment gap of more than 30 days.[53]

Zhang et al. advanced the cost-sharing debate by examining several different measures of medication adherence, focusing on the first 6 months of treatment and evaluating a wide range of cost-sharing amounts ranging from $0 to $128 per 30-day supply. However, the value of Zhang et al.'s study, like that of all other cross-sectional analyses of cost-sharing, was limited by the potential effect of unmeasured factors on study outcomes. Higher cost-sharing levels could be associated with unmeasured tangible factors (e.g., utilization management programs such as step therapy or prior authorization, formulary differences, or scope of pharmacy and physician networks) and intangible factors (e.g., organizational culture, patient educational efforts that could have taken place years before, or local practice patterns). These factors, not the cost-sharing levels themselves, could be largely responsible for the differences observed between higher and lower cost-sharing groups.[45,46]

Because of the extreme vulnerability of cross-sectional design to the effects of confounding factors, overall measures of quality of statistical models (e.g., measures of percentage of variance explained such as R-squared and pseudo-R-squared or predictive accuracy measures such as area under the Receiver Operating Characteristic curve) are particularly critical when using this design. These overall quality measures demonstrate the degree to which the models have accurately accounted for confounding factors in comparing outcomes across cross-sectional groups. For this reason, the current tendency among authors of cross-sectional studies to fail to report accepted measures of quality for their statistical models is unfortunate.[36-43] Although Zhang et al. are to be commended for reporting goodness-of-fit measures for their models, they indicate that the percentage of variance explained by their PDC model was only 9%. Thus, 91% of the variance in their measure of adherence was explained by unmeasured factors.[53]

In the November/December 2007 issue of *JMCP*, Klepser et al. provided a rare look at the outcomes of a change from a 3-tier copayment structure ($10/$25/$40 for generic/preferred brand/non-preferred brand) to a 25% coinsurance pharmacy benefit design with minimum and maximum OOP outlays per prescription.[54] Beneficiaries who experienced no change in the 3-tier copayment levels served as a comparison group. Using a difference-in-difference analysis, Klepser et al. found that from the pre-intervention to post-intervention period, total spending increased 6.3% in the intervention group and 9.5% in the comparison group for a relative difference of $1.30 per member per month (PMPM). However, overall prescription drug utilization (number of claims) did not differ significantly across intervention and comparison groups. From the pre-intervention to the post-intervention period, utilization per patient per month (PPPM) in 3 essential drug classes (antihypertensives, antidepressants, and statins) increased 4.1% in the intervention group versus 9.0% in the comparison group ($P=0.004$), and total expenditures in the 3 classes for the intervention and comparison groups increased by 8.2% ($5.07 PPPM) and 13.3% ($7.80 PPPM), respectively ($P=0.003$). However, the increases in employer cost for the 3 essential drug classes in the intervention group (7.5%, $2.86 PPPM) and comparison group (16.1%, $5.67 PPPM) did not differ ($P=0.057$).[54]

Klepser et al. advanced the cost-sharing debate by using a strong quasi-experimental (pre-period to post-period with comparison group) research design to assess an extremely understudied benefit structure and by explaining the potential impact of specific minimum and maximum OOP outlays per prescription on the outcomes assessed by their study. However, the coinsurance group assessed by Klepser et al.'s study did not experience a change in overall cost-share relative to the comparison group; increases in beneficiary cost from the pre-intervention to post-intervention periods were not significantly different for the intervention (7.5%) and comparison (3.0%) groups ($P=0.983$). Thus, the Klepser et al. study does not shed light on the effect of simultaneous benefit design change and an increase in the overall magnitude of beneficiary cost-share.

Protecting Home Plate: What Must We Do Now?

As Klepser et al. suggest, comparisons of different types of cost-sharing changes are needed. Changes from a 3-tier copayment plan to coinsurance structures with various amounts of cost-sharing increase are unstudied. Also unexplored in the peer-reviewed research literature is whether different forms of cost-sharing increase that achieve the same overall cost-sharing levels (e.g., increasing copayments in a 3-tier plan vs. increasing coinsurance rates) produce different outcomes; for example, prescription drug and medical utilization and cost, adherence to chronic medication therapy, or use of expensive services such as hospitalizations and emergency department visits.

Well-designed studies that directly measure the effect of cost-sharing decreases represent a more urgent need. Under the early cost-sharing paradigm, controlled studies of cost-sharing increases were the most appropriate way to inform the constantly evolving pharmacy benefit design process; these studies directly assessed the question of how consumers respond to rising prices for prescription medications. Conversely, under the new cost-reduction paradigm, we need controlled (at least quasi-experimental, preferably randomized) studies to document how consumers behave when their OOP outlays decline. Until the results of high-quality investigations of cost-sharing reductions become available to inform policymaking in this critical area, we risk the loss of the well-documented gains made in cost-sharing design over the past several decades (Table). Decision makers who reduce prescription drug copayments in hopes of better adherence and lower medical costs do so without the benefit of research evidence about how patients

actually respond to OOP cost reductions, making it especially important to monitor the clinical and economic outcomes of these reductions.

The Center for Value-Based Insurance Design (VBID), whose founders oppose CDHC and have long advocated determination of copayment levels based on medical need (e.g., reducing statin copayments for patients with higher cardiac risk), is currently involved in several research projects assessing VBID's impact on quality and cost.[55] Aetna, whose subsidiary ActiveHealth helps clients identify high-risk members for interventions (e.g., reduced copayments), plans a randomized trial of the effect of providing free medication in specified therapeutic classes (e.g., beta-blockers, statins) to patients who have had a myocardial infarction; a control group of patients will receive usual coverage and services.[2]

Meanwhile, the very limited evidence available to date does not support the view that reducing or eliminating prescription drug OOP cost will produce desired behavioral changes and even suggests that conclusions based on cross-sectional work may be incorrect. Karter et al.'s independent (not pharma-supported) quasi-experimental study of patients with diabetes mellitus assessed the effects of cost-sharing policy changes for glucose testing strips.[56] Under a policy of charging copayments for the test strips, Karter et al. documented a cross-sectional association between copayment amount and lower levels of test strip utilization. However, a new policy providing test strips free of charge did not increase test strip utilization, even among those with higher cost-sharing amounts prior to the change. The authors concluded that providing the free test strips had "shifted costs from patient to health plan, without improving adherence."[56]

TABLE *Key Features and Findings of Cost-Sharing Research in Insured Populations and Large Diverse Databases*[a]

Authors and Organizations	Design and Outcome(s)	Subjects	Key Findings	Sponsorship
		STUDIES PUBLISHED PRIOR TO 2002		
RAND Health Insurance Experiment team[3-5]	Experimental. Numerous outcomes. Key outcomes were total expenditures for health care and prescription drugs and a variety of health outcomes measures.	2,750 families randomized to 1 of 5 cost-sharing plans: (1) free of charge, (2) at a 25%, 50%, or 95% coinsurance rate for all services, or (3) at 95% coinsurance for outpatient services with free hospital inpatient care. Maximum annual OOP cost was indexed to family income; families received lump-sum payments for participation.	• Expenditures decreased at higher cost-sharing levels; health care costs and prescription drug costs were 57% higher and 60% higher, respectively, for free care than for 95% coinsurance enrollees. • Free-care enrollees used more medical care than did enrollees in higher cost-sharing arrangements, but did not have better outcomes. The only exceptions were low-income enrollees with certain chronic conditions. • Satisfaction with health care was generally high and unrelated to cost-sharing amount. • Enrollees in higher cost-sharing arrangements were less likely to worry about their health and had fewer restricted-activity days (including time spent in medical care) than did those receiving free care.	U.S. Department of Health and Human Services
Motheral and Fairman (Express Scripts)[13]	Pseudo-experimental (pre-post with comparison group); compared 12-month periods before and after implementation of copayment change. Outcomes were total drug cost, net insurer cost, number of prescription drug claims, rates of continuation with chronic medication therapy, use of antibiotics following a diagnosis of otitis media, and medical utilization (office visits, ER visits, and inpatient hospitalizations).	Intervention group whose employer switched from a 2-tier ($7/$12) to 3-tier ($8/$15/$25) structure (n = 6,881) in 1998. Comparison group whose employer retained a 2-tier ($7/$12) structure (n = 13,279).	• From the pre-implementation period through the first year post-implementation, payer's cost net of member copay grew by 3% in the intervention group and by 24% in the comparison group. • In the first year post-implementation, non-formulary medication use declined in the intervention group. Growth in total prescription claims was modestly lower in the intervention group than in the comparison group. • Study groups did not significantly differ in medication continuation rates for oral contraceptives, antihypertensives, or antihyperlipidemics. Continuation rates for estrogens were lower in the intervention group than in the comparison group at 6 months (91% vs. 87%) and at 11 months (84% vs. 76%), but discontinuation could not be linked to non-formulary drug use. • Study groups did not differ in use of antibiotics for otitis media. • Study groups did not significantly differ in use of any medical services measured.	No external sponsorship

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Authors and Organizations	Design and Outcome(s)	Subjects	Key Findings	Sponsorship
Motheral and Henderson (University of Arizona and Express Scripts)[12]	Quasi-experimental (pre-post with comparison); compared periods 6 months before and 6 months after copayment change. Outcomes were measures of (1) prescription drug utilization and expenditures; (2) continuation with chronic medication; and (3) outcomes by medication type.	Age- and gender-matched samples of intervention (change from either $4/$10 to $5/$15 or $5/$10 to $7/$15) and comparison ($5/$10) plans; n = 1,112 adults (age ≥ 18 years) in both groups.	• In the 6 months following the copayment change, total drug expense declined by $18 PMPM in the intervention group and increased by $31 PMPM in the comparison group. • Brand cost decreased by $6 in the intervention group and increased by $34 in the comparison group. • Generic fill rate increased by 1 percentage point in the intervention group and declined by 6 percentage points in the comparison group. • Rates of continuation with chronic medications were not related to the copayment change.	No external sponsorship
STUDIES PUBLISHED IN 2002				
Joyce et al. (RAND Health)[38]	Cross-sectional, statistical controls.[b] Outcomes were drug costs, overall and for generic, single-source brand and multisource brand; costs for payers and OOP beneficiary cost.	420,786 beneficiaries aged 18-64 years enrolled at any time from 1997 to 1999 (claims database, 25 employers).	• Predicted (statistically adjusted) PMPY drug spending was $725 for a single-tier plan with a $5 copayment, $678 for a 2-tier plan with $5/$10 copayments, $666 for a 3-tier plan with $5/$10/$15 copayments, and $436 for a 3-tier plan with $10/$20/$30 copayments. • Predicted annual patient OOP cost was $123 for a single-tier plan with a $5 copayment, $119 for a 2-tier plan with $5/$10 copayments, $134 for a 3-tier plan with $5/$10/$15 copayments, and $141 for a 3-tier plan with $10/$20/$30 copayments. • Predicted annual health plan cost was $602 for a single-tier plan with a $5 copayment, $559 for a 2-tier plan with $5/$10 copayments, $532 for a 3-tier plan with $5/$10/$15 copayments, and $295 for a 3-tier plan with $10/$20/$30 copayments.	California Healthcare Foundation
STUDIES PUBLISHED IN 2003				
Fairman et al. (Express Scripts)[15]	Pseudo-experimental (pre-post with comparison group); analyses compared 12-month pre-implementation period with 30-month post-implementation follow-up. Outcomes were total drug cost, net insurer cost, number of prescription drug claims, rates of continuation with chronic medication therapy, and medical utilization (office visits, ER visits, and inpatient hospitalizations).	Intervention group whose employer switched from a 2-tier ($7/$12) to a 3-tier ($8/$15/$25) structure on (n = 3,577) in 1998. Comparison group whose employer retained a 2-tier ($7/$12) structure (n = 4,132).	• From the pre-implementation period through the second year post-implementation, payer's cost net of member copay grew by 30% in the intervention group and 57% in the comparison group. • In the first year post-implementation, non-formulary medication use declined in the intervention group. Growth in total prescription claims was modestly lower in the intervention group than in the comparison group. • Study groups did not significantly differ in medication continuation rates for estrogens, antihypertensives, or antihyperlipidemics. Continuation rates for oral contraceptives were lower in the intervention group (66%) than in the comparison group (79%) at 6 months but not at any other time during follow-up. • Study groups did not significantly differ in use of any medical services measured.	No external sponsorship
Huskamp et al. (Harvard Medical School, Brigham and Women's Hospital, Medco Health Solutions [Merck & Co.[c]])[14]	Quasi-experimental (pre-post with comparison group); analyses compared pre-implementation and post-implementation periods that were each "more than one year" in duration. Outcomes were probability of use, total spending, rates of discontinuation, and rates of switching for 3 drug classes.	Users of PPIs, statins, and ACEIs in 2 employer groups. Employer 1 changed from a single-tier ($7) to a 3-tier ($8/$15/$30) benefit. Employer 2 changed from a 2-tier ($6/$12) to a 3-tier ($6/$12/$24) benefit. Comparison groups for Employers 1 and 2 made no copayment changes to designs of $8/$15 and $6/$12, respectively.	• Probability of use was lower for the copayment change group than for the comparison group for Employer 1 (dramatic copayment change) but not for Employer 2 (modest copayment change). • The plan's drug expenditures dropped and enrollee expenditures increased for both employers, but these trends were more pronounced for Employer 1. • Users of non-preferred (tier 3) drugs subject to a $12 copayment change (Employer 2) were more likely to switch to preferred drugs but were not more likely to discontinue therapy than were comparison patients in the 6 months following the change. • Users of non-preferred (tier 3) drugs subject to a $23 copayment change were more likely to discontinue therapy than were comparison patients in the 6 months following the change.	Robert Wood Johnson Foundation, National Institute of Mental Health, AHRQ

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Authors and Organizations	Design and Outcome(s)	Subjects	Key Findings	Sponsorship
Nair et al. (University of Colorado, Wolfe Statistical Consulting, University of Iowa, Anthem Blue Cross Blue Shield of Colorado)[16]	Quasi-experimental (pre-post with comparison); analyses compared 7 month pre-change versus 7 month post-change period. Mean prescriptions PPPM, generic use rate, formulary compliance rate, MPR, discontinuation of non-formulary medication (whether patient discontinued therapy or switched to a formulary medication was not measured).	8,132 patients who filled prescriptions for ≥ 1 of 5 disease states (hypertension, dyslipidemia, arthritis, diabetes, gastroesophageal reflux disease) during the 5 months prior to a copayment change. Intervention group changed from a 2-tier to a 3-tier benefit (n = 5,710). Comparison groups remained 2-tier (n = 715) or remained 3-tier (n = 1,707).	• Formulary compliance rate increased by 5.6% for the copayment change group but did not significantly increase for the comparison group. • Generic fill rate increased for all 3 study groups—4.9 percentage points for the copayment change group, 4.8 percentage points for the 2-tier comparison group, and 3.3 percentage points for the 3-tier comparison group. • Rates of discontinuation of non-formulary medications were higher for copayment change groups than for comparison groups (odds ratios 1.76 vs. 2-tier comparison group and 1.49 vs. 3-tier comparison group); however, authors noted that predictive ability of logistic regression model was poor (c-statistic = 0.57).	Merck & Co.
Rector et al. (UnitedHealth Group, Wharton School)[17]	Longitudinal with comparison groups (tiered vs. non-tiered); however, the point in time at which tiered copayment was instituted was not measured, making it difficult to assess effects of change. Change from 1998 to 1999 in percentage of prescriptions that were for preferred brand products.	Prescriptions for medications in selected classes (ACEIs, PPIs, statins) in 4 health plans (188 employers) using the same formulary; some groups instituted tiered copayments at unmeasured points in time (for an unknown number, this change occurred before the start of the study period), while other groups did not have tiered copayments.	• Between-group (tiered vs. non-tiered) differences in percentage change amounts for ACEIs, PPIs, and statins were 17.3%, 8.4%, and 12.7%, respectively. • Logistic regression analyses estimated increases in the probability of preferred brand use associated with tiered copayments; estimated increases were 13.3, 8.9, and 6.0 percentage points for ACEIs, PPIs, and statins, respectively. • Logistic regression analyses explained only 1.4%-3.6% of the variance in preferred brand use.	AstraZeneca Pharmaceuticals
STUDIES PUBLISHED IN 2004				
Briesacher et al. (University of Massachusetts, University of Maryland, Novartis, AstraZeneca, Merck & Co., TAP)[43]	Cross-sectional, statistical controls.[b] Outcome was rates of use for COX-2 inhibitors (vs. nonselective NSAIDs).	20,868 patients in employer-sponsored plans, with osteoarthritis or rheumatoid arthritis and ≥ 1 claim for NSAID or COX-2 inhibitor during the year 2000 (MarketScan Database).	• COX-2 inhibitor use rates were 63.0%, 53.6%, and 41.6%, respectively, in single-tier, 2-tier, and 3-tier plans. • Generic NSAID use rates were 37.7%, 40.7%, and 55.7%, respectively, in single-tier, 2-tier, and 3-tier plans. • Among patients with diagnoses indicating gastrointestinal complications risk, a 3-tier formulary decreased the likelihood of COX-2 inhibitor use by approximately 50%.	Novartis
Ellis et al. (University of Michigan, Vanderbilt University)[41]	Cross-sectional, statistical controls.[b] Outcomes were percentage of statin treatment days without medication (gap) and statin discontinuation rates from the date of the first statin fill until a switch to a non-statin antihyperlipidemic, death, disenrollment or end of data availability.	Adults who filled ≥ 2 statin prescriptions from January 1998 to November 2001 (single MCO and university-affiliated hospital in the Midwest); sample was split into primary (n = 2,544) and secondary (n = 2,258) prevention patients.	• For primary and secondary prevention groups, gap percentages were 20.4% and 21.5%, respectively. • Compared with patients whose average monthly copayment was < $10, patients with copayments of $10 to < $20 and ≥ $20 had higher rates of discontinuation (hazard ratios of 1.39 and 4.30, respectively). Adherence rates were similarly lower for patients with higher average monthly copayment.	Sponsorship not described
Goldman et al. (RAND Health, Merck & Co., California Healthcare Foundation)[37]	Cross-sectional, statistical modeling.[b] Outcome was number of drug days supplied.	528,969 privately insured beneficiaries aged 18-64 years, enrolled from 1 to 4 years during 1997-2000 (database of 52 health plans).	• Statistically modeled doubling of copayments in a "prototypical drug benefit plan" was associated with use reductions in 8 therapeutic classes. • Modeled decreases associated with a hypothetical doubled copayment were 45% for NSAIDs, 44% for antihistamines, 34% for antihyperlipidemics, 33% for antiulcer drugs, 32% for antiasthmatics, 26% for antihypertensives, 26% for antidepressants, and 25% for antidiabetics. • Modeled decreases were smaller for patients with ≥ 2 medical claims indicating a chronic illness.	California Healthcare Foundation, Merck & Co., and AHRQ

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Authors and Organizations	Design and Outcome(s)	Subjects	Key Findings	Sponsorship
STUDIES PUBLISHED IN 2005				
Landsman et al. (Wellpoint Pharmacy Management, Merck & Co.)[18]	Quasi-experimental (pre-post with comparison); compared periods 12 months pre-change with 12 months post-change. Outcome measures were MPRs, rates of switching to lower-copayment products, discontinuation rates, and price elasticity.	Users of 9 commonly used therapeutic classes enrolled in plans that (1) changed from $5/10 to $5/$15/$25 (n = 30,000); (2) changed from $10/$20 to $10/$20/$40 (n = 400,000); (3) changed from $5/$10 to $5/$20/$35 (n = 200,000); and (4) made no change to a $10/$20 structure (n = 1,000,000); authors excluded 20% of potential sample for copayment discrepancies, including "grandfathering" of initial post-implementation fill.	• MPRs declined in the intervention group by "statistically significant but modest" amounts (largest change was –6.8% for NSAIDs) but remained more than 80% for all cardiovascular medication classes. • Drug switch rates were higher for intervention than for comparison patients among users of calcium channel blockers, statins, NSAIDs, and triptans, but not among users of ACEIs, ARBs, COX-2 inhibitors, SSRIs, or TCAs. • Discontinuation rates were significantly higher for intervention group patients than for comparison group patients among users of ACEIs, ARBs, statins, SSRIs, and TCAs; however, this analysis counted switches from ACEIs to ARBs and from ARBs to ACEIs as discontinuations and included patients whose most recent claim was ≥ 3 months prior to the copayment change. • For the subset of patients with ≥ 2 claims within the 3 months prior to the change, prescription-filling behavior was inelastic (not price sensitive).	Merck & Co.
STUDIES PUBLISHED IN 2006				
Roblin et al. (Kaiser Permanente, Harvard Medical School, Harvard Pilgrim Health Care, HealthPartners Research Foundation, Fallon Health Care)[26]	Quasi-experimental (time series with comparison group); analyses compared 6 month periods prior to and following copayment changes ranging from $1 to ≥ $10 for a 30-day supply of oral hypoglycemic (OH) medication. Outcome measure was OH average daily dose (ADD).	Enrollees of 5 managed care organizations aged ≥ 19 years, with ≥ 4 months of OH use during the 6 months pre-change and ≥ 1 filled OH prescription for the same OH medication during the 6 months post-change; 12-month episodes were split by cost-sharing increase levels: $1-$6 (n = 11,975), $7-$10 (n = 904), and > $10 (n = 231).	• Cost-sharing increases of $1-$10 were unrelated to ADD of OH. • Increases of > $10 were associated with a decline of 2.6% per month in ADD. • For episodes with a cost-sharing increase of > $10, at 6 months after the increase, OH ADD was 18.5% less than expected based on pre-change trend. • However, < 2% of the study sample experienced a copayment change of > $10, and of that group 69% had received OH medication either free of charge or for < $5 per month prior to the change.	AHRQ
Gibson et al. (Thomson MedStat, Pfizer)[36]	Cross-sectional time series (unit of analysis was the person-month), statistical controls.[b] Outcome was MPR for statins.	New (n = 142,341) and continuing (n = 92,344) statin users identified during 2000-2003 (MarketScan Database).	• Higher copayments were associated with lower statin adherence rates. • A 100% change in index copayment was associated with a 2.6 percentage point decline in adherence among new users and a 1.1 percentage point decline among continuing users.	Pfizer
Goldman et al. (RAND Health)[42]	Cross-sectional, statistical modeling.[b] Outcomes were (1) MPR for cholesterol-lowering (CL) therapy in the first year and (2) use of hospitalizations and ER visits in subsequent years.	62,274 patients aged ≥ 20 years who initiated CL therapy (no use of CL therapy in prior 6 months) from 1997 to 2001 (claims database, 88 health plans, 25 employers).	• Higher copayment levels were associated with reduced adherence; mean compliance rates were 5 percentage points lower when copayments were $10 higher. • The modeled full compliance percentage was 6-10 percentage points lower for patients with $20 copayments than for patients with $10 copayments. • For each 1,000 patients classified as "high risk" based on age, sex, and comorbid conditions, modeled hospitalization counts were 643 for fully compliant patients and 1,000 for partially compliant patients. • A simulated policy eliminating copayments for high- and medium-risk patients and raising copayments for low-risk patients would "avert 79,837 hospitalizations and 31,411 ER visits annually," assuming 6.3 million U.S. adults on CL therapy.	National Institute on Aging and UCLA Claude D. Pepper Older Americans Independence Center
Taira et al. (Hawaii Medical Service Association, Novartis)[39]	Cross-sectional; statistical controls.[b] Outcome was MPR; compliance was defined as MPR ≥ 80%.	114,232 patients who had ≥ 1 medical claim with a diagnosis of hypertension and filled ≥ 1 antihypertensive medication prescription between January 1999 and June 2004 (managed care organization with 650,000 lives). Patients were grouped by tier (tier 1 = $5, tier 2 = $20, tier 3 = difference between preferred and nonpreferred [range $20-$165]). Patients who switched tiers were counted in multiple tier categories.	• MPRs were 66.8% for tier 1 (n = 58,809), 66.1% for tier 2 (n = 66,486), and 53.6% for tier 3 (n = 60,553). • Adjusted odds ratios for compliance were 0.76 for medications in tier 2 and 0.48 for medications in tier 3 (reference category was medications in tier 1).	Novartis

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STUDIES PUBLISHED IN 2007				
Karter et al. (Kaiser Permanente Northern California ([KPNC])[56]	Quasi-experimental (pre-post with comparison group); glucose test strips were provided first for a copay, then free, then for 20% coinsurance. Outcome measure was utilization of glucose testing strips.	Subjects with diabetes mellitus, identified from KPNC's diabetic registry of approximately 132,000 patients in 15 hospitals and 23 outpatient clinics.	• Initial cross-sectional analysis during the copayment period indicated inverse relationship between copayment amount and test strip use. • A new policy of providing free test strips did not increase utilization, even among patients paying higher copayment amounts before the change. • Institution of coinsurance resulted in statistically significant, but not clinically significant, reductions in test strip use.	No external sponsorship
Zhang et al. (University of Minnesota, Data Intelligence Consultants, Prime Therapeutics LLC, BlueCross BlueShield of Minnesota)[53]	Cross-sectional. Outcomes were 3 measures of medication adherence.	New users (N = 1,351) of single-agent ACEIs or ARBs between January 1, 2004, and June 30, 2004; copayment amounts ranged from $0 to $128 per 30-day supply.	• Each $1 in additional member cost-share for the initial prescription claim was associated with (1) a 2.8% greater odds of being nonpersistent at 6 months after initiating therapy; (2) a 1.9% increase in total days of gap (days without medication); and (3) a 1.0% increase in the risk of having a treatment gap of > 30 days.	No external sponsorship
Klepser et al. (University of Nebraska, BlueCross BlueShield of Nebraska)[54]	Quasi-experimental (pre-post with comparison group); difference-in-difference analysis compared 6-month time periods before and after institution of a 4-tiered 25% coinsurance with minimum and maximum amounts at each tier. Outcomes were drug expenditure PMPM (overall, employer, and patient OOP) and claims PMPM; outcomes were measured for all drugs and for 3 essential medication classes.	Adult (aged ≥ 18 years) enrollees of a managed care organization in the Midwest from September 1, 2004, through March 31, 2006. Intervention plan changed from 3-tier copayment ($10/$25/$40) to coinsurance (n = 46,311). Comparison plan retained the $10/$25/$40 structure (n = 7,916). The percentage of total cost paid OOP by the beneficiary was approximately 32% in both groups and did not change significantly after coinsurance implementation.	• From pre-intervention to post-intervention, total PMPM drug expenditure increased 6.3% in the intervention group and 9.5% in the comparison group, for a relative difference of $1.30 PMPM. • Prescription drug utilization did not differ significantly across intervention and comparison groups. • From pre-intervention to post-intervention, PPPM utilization of 3 essential drug classes (antihypertensives, antidepressants, and statins) increased 4.1% in the intervention group versus 9.0% in the comparison group; total expenditures increased by 8.2% and 13.3%, respectively. • Increases in employer cost for the 3 essential drug classes in the intervention and comparison groups did not differ.	No external sponsorship

[a] *Chart does not include studies limited to special populations (e.g., mentally ill, low-income, government-sponsored health insurance, elderly). Chart includes only studies with cross-sectional, experimental, or quasi-experimental designs.*

[b] *Indicates that study authors did not present standard statistics (e.g., area under the Receiver Operating Characteristic curve, R-squared, pseudo-R-squared) documenting the adequacy of the statistical model.*

[c] *Medco was a subsidiary of Merck & Co. until August 2003.*

ACEI = angiotensin-converting enzyme inhibitor; ADD = average daily dose; AHRQ = Agency for Healthcare Research and Quality; ARB = angiotensin II receptor blocker; CL = cholesterol-lowering; COX-2 = cyclooxygenase-2; ER = emergency room; MCO = managed care organization; MPR = medication possession ratio; NSAID = nonsteroidal anti-inflammatory drug; OH = oral hypoglycemic; OOP = out-of-pocket; PMPM = per member per month; PMPY = per member per year; PPI = proton pump inhibitor; PPPM = per patient per month; TCA = tricyclic antidepressant; SSRI = selective serotonin reuptake inhibitor.

As this article was going to press, a purportedly controlled analysis, co-sponsored by 2 pharmaceutical manufacturers, showed improved adherence (MPR increase of ≤ 4 percentage points for ACEIs and ARBs, beta-blockers, statins, and diabetes drugs) for a large employer that reduced OOP costs compared with another employer that made no OOP cost reduction. However, the study report did not disclose key baseline utilization measures for the intervention and comparison employer groups, whose mean ages differed by > 6 years (37.4 vs. 43.9, respectively) and whose copayment structures appeared markedly different even prior to the change (e.g. for generics $5 flat copayment vs. $16.22 average, respectively).[57] Clearly this research is in its nascence; randomized studies or analyses of more comparable groups are urgently needed.

Our Challenge Today

This is a moment of opportunity, in which the health insurance industry will choose to base its decisions about cost-sharing on evidence directly linked to proposed policies or implement unproven designs based on a hoped-for but untested "home run" improvement to the cost-sharing paradigm. Policymakers will do well to understand that in cost-sharing benefit designs, research methods matter. In making a decision about whether to implement a cost-sharing change, it is appropriate to give more

credence to studies that directly measure the effect of a similar change. For example, if a cost-sharing decrease is being considered, the best and most informative research is a controlled study (i.e., a design that includes a control or comparison group) of a cost-sharing decrease, preferably in a similar population (e.g., same type of insurance, similar age and gender profile, similar industry). Much less weight should be accorded to studies that measure only associations between cost-sharing levels and patient outcomes. Studies that report statistically controlled associations but fail to report key measures of the adequacy of those statistical controls should be given little or no consideration.

It took the Red Sox 18 years to recover the opportunity that was lost in 1986, and in 2004 the team finally won a World Series title. Yet in the health care field, massive system-wide changes to health care financing and delivery are being proposed at a pace that should give pause to advocates of evidence-based decisions. These changes have the potential to affect not only outcomes for individual patients, but also the viability of the health care financing system—whether publicly or privately funded—to sustain affordable coverage for necessary services in the years to come. Like the Boston Red Sox, the health insurance industry may take far too many years to make up for our error if we miss the opportunity to measure the impact of these cost-sharing and benefit design proposals now.

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