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REFERENCE

Born in 1963, Sean McCabe grew up in San Diego, California. His family moved to Minneapolis, Minnesota, when he was a teenager, and he completed his last 2 years of high school there. He attended the College of Visual Arts in St. Paul for a while, then moved west to Utah to live near Duffy McCabe, one of his brothers. After that, he traveled for a year, trekking and climbing through Nepal and Pakistan. He returned to Utah in the late 1980s and earned his bachelor of fine arts degree from the University of Utah in Salt Lake City. Following graduation, he enrolled in the University's education program and received his teaching certificate. McCabe was an art teacher, fine artist, and graphic designer. His artwork appeared in such magazines as Cross Country Skier, American Alpine Journal, Climbing, and Alpinist. McCabe's graphic designs can be seen on the clothing labels of The North Face, Patagonia, and Black Diamond. In the 15 years that he resided in Mazama, Washington, a small village resting at the foot of the Cascade Mountains in the Methow Valley, he participated in activities such as cross-country skiing, hiking, and rock climbing. McCabe's outdoor interests are clearly evident in his vibrant oil paintings and woodblock prints. On the Sean McCabe website (seanmccabestudio.com), his work has been divided into 3 appropriate sections: the Landscape Gallery, the Skiing Gallery, and the Climbing Gallery. He was truly a unique artist with a colorful, and sometimes whimsical, style.

In November 2009, at the age of 46, McCabe lost his battle with anaplastic thyroid carcinoma, a rare and aggressive cancer. His journey was documented on the CaringBridge website (caringbridge.org/visit/seanmccabe). McCabe wrote a few entries on the journal segment of the site himself, including this message about his faith, his wife, Laura, and daughters, Novie and Dashe: “I can trust God, He has given me so much over the years—my wife and best friend of over 23 years, two beautiful and healthy girls, and a position in a community in which I can serve people.”

On November 15, 2009, a memorial service for McCabe was held at the school where he taught, Liberty Bell Junior-Senior High School in Winthrop, Washington. The audience of 1,200 both wept and laughed during the service. One of the walls in the auditorium was covered with messages from his students, and his painting of Liberty Bell Mountain that he donated to the school was on display. Many of the speakers at the memorial talked about the beloved teacher's ability to make everyone feel special. Liberty Bell's principal, Debra DeKalb, read a quote that McCabe wrote in 2008 when asked to describe the ideal student-teacher relationship: “Make every student feel like they are the most important person in our life—love (try to love) each individual student as if they were your own child. Protect them, encourage them, challenge them, provide for them, edify them, critique them, listen to them, and include them.”

During his career, McCabe received numerous teaching awards, such as “Teacher of the Year” in both Utah and Washington. He was awarded the prestigious Catalyst Award in 2000, which was a precursor to his national recognition in 2001 with The Milken Family Foundation Award, one of education's most prestigious honors.

McCabe was featured in “The Fine Art of Skiing” article in the December 2008 issue of Cross Country Skier magazine, the oldest journal on recreational Nordic skiing in the world. The artist said that he created his paintings as a way of sharing his outdoor adventures with others. McCabe went on to describe his work as expressionistic: “I take liberties with the human form and with color,” he said. “My figures are almost character-like, perhaps similar in style to Thomas Hart Benton’s depiction of the American worker in many of his paintings.” Most of McCabe’s compositions show the relationship between Man and Nature in the form of figures juxtaposed against the mountains, and many of them were painted from a skier’s perspective. “My skiers represent me, my friends or experiences …,” he said.

McCabe’s After the Storm painting depicts a lone cross-country skier exploring a trail in freshly fallen snow. Although he did not illustrate the sun in this picture, one can perceive the scene’s intense sunlight because of the brightness of the snow and the dramatic shadows cast by the trees. The skier is headed uphill, which could symbolize human struggles and frailties.

Thankfully, the artist’s inspirational visions of the Cascade Mountain range and its people live on in his paintings, prints, and graphic designs. Laura McCabe, a past Olympian in Nordic skiing and present cross-country ski coach, maintains the Sean McCabe website. She says that some of his original paintings are still available for sale. The site also offers prints of McCabe’s work in many different sizes in the form of canvas transfers or traditional prints on paper.

Sheila Macho
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ACE Inhibitor and ARB Utilization and Expenditures in the Medicaid Fee-For-Service Program from 1991 to 2008

Boyang Bian, MS; Christina M.L. Kelton, PhD; Jeff J. Guo, PhD; and Patricia R. Wigle, PharmD

ABSTRACT

BACKGROUND: Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) are widely prescribed for the treatment of hypertension and heart failure, as well as for kidney disease prevention in patients with diabetes mellitus and the management of patients after myocardial infarction.

OBJECTIVE: To (a) describe ACE inhibitor and ARB utilization and spending in the Medicaid fee-for-service program from 1991 through 2008, and (b) estimate the potential cost savings for the collective Medicaid programs from a higher ratio of generic ACE inhibitor utilization.

METHODS: A retrospective, descriptive analysis was performed using the National Summary Files from the Medicaid State Drug Utilization Data, which are composed of pharmacy claims that are subject to federally mandated rebates from pharmaceutical manufacturers. For the years 1991-2008, quarterly claim counts and expenditures were calculated by summing data for individual ACE inhibitors and ARBs. Quarterly per-claim expenditure as a proxy for drug price was computed for all brand and generic drugs. Market shares were calculated based on the number of pharmacy claims and Medicaid expenditures.

RESULTS: In the Medicaid fee-for-service program, ACE inhibitors accounted for 100% of the claims in the combined market for ACE inhibitors and ARBs in 1991, 80.6% in 2000, and 64.7% in 2008. The Medicaid expenditure per ACE inhibitor claim dropped from $37.24 in 1991 to $24.03 in 2008 when generics accounted for 92.5% of ACE inhibitor claims; after adjusting for inflation for the period from 1991 to 2008, the real price drop was 59.2%. Brand ACE inhibitors accounted for only 7.5% of the claims in 2008 for all ACE inhibitors but 32.1% of spending; excluding the effects of manufacturer rebates, Medicaid spending would have been reduced by $28.7 million (9%) in 2008 if all ACE inhibitor claims were generic. The average price per ACE inhibitor claim in 2008 was $24.03 ($17.64 per generic claim vs. $103.45 per brand claim) versus $81.98 per ARB claim. If the 7.5% of all ACE inhibitor claims that were brand in 2008 were substituted with generic ACE inhibitors, the average price per ACE inhibitor claim declined from approximately $37 in 1991 to $24 in 2008, while the average price for ARB claims increased from approximately $38 in 1995 to $82 in 2008.

What is already known about this subject

- Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) are both widely used in the treatment of hypertension and heart failure and in the prevention of macrovascular and microvascular cardiovascular outcomes associated with hypertension and diabetes. In 2009, ACE inhibitors were the fourth most utilized drug class in the United States with 162.8 million prescriptions, and ARBs were the eleventh most utilized drug class with 82.5 million prescriptions.
- Utilization of ACE inhibitors and ARBs may be cost-effective for their approved indications particularly when generic drugs are used in place of brand name drugs. Captopril was the first generic ACE inhibitor at year-end 1995, but it was almost 5 years before the class became relatively inexpensive with the introduction of generic enalapril in 2000 Q3 and lisinopril in 2002 Q3. The first generic ARB (losartan and losartan/HCTZ) entered the U.S. market in April 2010.

What this study adds

- In 2008, state Medicaid fee-for-service programs spent approximately $310 million for both ACE inhibitors ($108 million) and ARBs ($202 million). ARBs represented only 35.3% of the total claims but 65.1% of the total combined expenditure because of the higher average price per claim, $81.98 for ARBs versus $24.03 for ACE inhibitors.
- With generic drug entry for the ACE inhibitors, the average price per ACE inhibitor claim declined from approximately $37 in 1991 to $24 in 2008, while the average price for ARB claims increased from approximately $38 in 1995 to $82 in 2008.
- If the 7.5% of all ACE inhibitor claims that were brand in 2008 were substituted with generic ACE inhibitors, the average price per claim would have been $17.64 rather than $24.03, representing a savings opportunity of $28.7 million (9%) for the Medicaid fee-for-service programs for combined ACE inhibitor-ARB spending. The total cost savings opportunity was as much as $142.3 million (46%), attainable with 100% generic ACE inhibitors and a 90% ratio of ACE inhibitors to total ARB and ACE inhibitors, associated with a reduction in the average price per claim from $44.52 to $24.07, excluding the effects of manufacturer rebate payments.
Hypertension is a major risk factor for the development of cardiovascular disease, including coronary artery disease, stroke, and heart failure. According to the American Heart Association, there were 74.5 million people with hypertension (representing a 33.6% adult prevalence rate) and 5.8 million with heart failure in the United States (a 2.6% adult prevalence rate) in 2006. In 2007, an estimated 17.5 million people in the United States were diagnosed with type 1 or type 2 diabetes, a disease that often coexists with hypertension.

Although thiazide-type diuretics are recommended as first-line therapy for uncomplicated hypertension, patients with stage 2 hypertension (systolic blood pressure equal to or greater than 160 mmHg) should be treated with a combination of 2 antihypertensive medications. Angiotensin-converting enzyme (ACE) inhibitors are widely used in the treatment of hypertension. Their effect on the renin-angiotensin-aldosterone system, combined with improved ventricular remodeling, make ACE inhibitors an attractive option for heart failure patients, as well as for patients who have had a myocardial infarction. Multiple effects on the kidney, including a decrease in renovascular resistance, make ACE inhibitors appropriate also for decreasing the progression of nephropathy in patients with diabetes. Labeled indications besides hypertension for the various ACE inhibitors include congestive heart failure; to improve survival following myocardial infarction; stable coronary artery disease; risk reduction for myocardial infarction, stroke, and death from cardiovascular causes; and left ventricular dysfunction after myocardial infarction.

The first ACE inhibitor, captopril (Capoten), was approved by the U.S. Food and Drug Administration (FDA) in 1981 to treat hypertension and enjoyed market exclusivity for almost 5 years until the second ACE inhibitor, enalapril (Vasotec), was introduced at the end of 1985. Following enalapril, a number of other brand ACE inhibitors entered the market (Table 1). The latest FDA-approved ACE inhibitor was trandolapril (Mavik) in 1996. Many of the ACE inhibitors are also marketed as combination drugs either with a diuretic (e.g., Lotensin-HCT; benazepril and hydrochlorothiazide [HCTZ]) or with a calcium channel blocker (e.g., Lotrel; benazepril and amlodipine). All of the ACE inhibitors now have generic equivalents in 2010. According to IMS Health, of 3.9 billion prescriptions dispensed in the United States in 2009, 162.8 million (4.2%) were for ACE inhibitors. Only 3 drug classes had more prescriptions dispensed in 2009: lipid regulators, codeine and combinations, and antidepressants.

Angiotensin receptor blockers (ARBs), a newer class of antihypertensives, are also widely prescribed either as monotherapy or in combination with a diuretic or calcium channel blocker. Along with hypertension, labeled indications for the ARBs include heart failure, nephropathy in type-2 diabetic patients, left ventricular hypertrophy, reduction in the risk of stroke, and reduction in cardiovascular mortality following a myocardial infarction. ARBs are also prescribed for patients who cannot tolerate an ACE inhibitor-induced cough. On April 14, 1995, the FDA approved the first ARB, losartan (Cozaar), for clinical use in the United States. Cozaar dominated the ARB market briefly (Table 1). The most recent FDA approval of an ARB was olmesartan (Benicar) in April 2002. Although none of the ARBs experienced generic entry during the study period, generic losartan and losartan/HCTZ have been available in the U.S. market since April 2010.

ARBs have not been shown to be more effective than ACE inhibitors in blood-pressure reduction or in slowing the progression of renal disease or slowing the progression to type-2 diabetes. ARBs are associated with a lower incidence of cough, but the absolute rates of cough are often low including the head-to-head trial of ramipril (4.2%) versus telmisartan (1.1%) in ONTARGET (Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial). In 2009, 82.5 million prescriptions were dispensed for ARBs (which represent approximately 2% of all U.S. prescriptions), and the ARB class was ranked eleventh in prescription volume. Cardiovascular mortality has been decreased by certain antihypertensive medications, including ACE inhibitors and ARBs.

Due to its high and rising prevalence, hypertension is an expensive disease. Moreover, the growing acceptance of ACE inhibitors and ARBs as first-line therapies in the treatment of hypertension coupled with a decline in cardiovascular disease mortality (leading to longer use of the antihypertensive medications) imply higher expenditures for drug treatment. A number of chronic disease conditions have propelled spending on prescription drugs, and Medicaid and Medicare combined spending on outpatient prescription drugs was over $70 billion in 2008, much higher than 2 decades ago (Figure 1). Although an abrupt drop in Medicaid expenditures accompanied the transfer of dual Medicaid-Medicare eligibles to Medicare Part D in 2006, an upward trend in Medicaid spending was seen between 2006 and 2008.

In response to rising prescription drug expenditures, state Medicaid programs have developed a variety of cost-containment strategies, including beneficiary cost sharing, preferred drug lists, formularies, requiring generic substitution, and prior authorization (PA) for certain types of medication. These strategies are not standardized, and each state has its own set of policies. Fischer and Avorn (2003) estimated that there were potential cost savings for Medicaid of $450 million from greater overall use of generic drugs. Due to the therapeutic interchangeability of ACE inhibitors and ARBs, coupled with the availability of inexpensive generic ACE inhibitors, many private payers require PA or step-therapy for ARBs. Hence, the present study has 2 objectives: (a) describe ACE inhibitor
and ARB utilization and spending in the Medicaid fee-for-service program from 1991 through 2008, and (b) estimate the potential cost savings for the Medicaid programs from a higher ratio of generic ACE inhibitor utilization.

**Methods**

A retrospective, descriptive analysis was performed for the years 1991-2008 using the publicly available National Summary Files from the Medicaid State Drug Utilization Data maintained by the Centers for Medicare & Medicaid Services. The database covers Medicaid beneficiaries in 49 states (all except Arizona) and the District of Columbia and is restricted to outpatient pharmaceuticals. The National Summary Files in the present study were compiled by aggregating state databases; the method is described in detail below. Since the data are collected as part of the Medicaid Rebate Program, they include fee-for-service but not managed Medicaid pharmacy claims. States differ in how their drug benefit programs are managed. Arizona, for example, is not included in the database because it is 100% managed care (i.e., Arizona Medicaid pharmacy claims are not eligible for federally negotiated manufacturer rebates). The database appeared to contain coding errors in 2006 (all quarters) and 2007 Q3. During those 5 quarters, for some individual drugs including ACE inhibitors and ARBs, expenditures were incorrectly reported; hence, using the utilization data, which seemed to be correctly reported, we re-estimated expenditures for these 5 calendar quarters. For example, taking an average of per-unit (e.g., individual capsule or tablet) expenditure (i.e., pharmacy reimbursement) for quarters before and after the quarter in which a coding error occurred, we multiplied that average by the number of units. In this way, we came up with pharmacy reimbursement estimates that had better face validity. The general results from the present study were not affected by this small amount of data cleaning.

Each data record included the National Drug Code (NDC) number, drug name (trade or generic), year and quarter of Medicaid expenditure, number of pharmacy claims, number of units (e.g., individual capsules or tablets), and total pharmacy reimbursement amount, including drug cost and dispensing fee. The first 5 digits of the NDC number identified the drug manufacturer, while the remaining digits identify specific drug product by strength, dose formulation, and packaging. We searched the database for all ACE inhibitors and ARBs using both trade name and generic name (Table 1). For each of the drugs in Table 1, and for the ACE inhibitor and ARB classes overall, quarterly claim counts and reimbursement amounts were calculated by summing data across individual NDCs for each of the drugs and then for each class of drugs, respectively. Data for all the generic versions of each drug were aggregated, and all the combination drugs (with diuretic or calcium channel blocker) were aggregated with their stand-alone counterparts (e.g., claims for lisinopril/HCTZ were combined with those for lisinopril). Market shares were calculated based on both number of prescriptions and Medicaid payments.

### Table 1

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brand Name</th>
<th>Brand Drug Manufacturer</th>
<th>FDA Approvala</th>
<th>First Quarter of Generic Entry</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ACE Inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Captopril</td>
<td>Capoten Capozide&lt;sup&gt;b&lt;/sup&gt;</td>
<td>BMS BMS</td>
<td>04/06/81 10/12/84</td>
<td>1995 Q4</td>
</tr>
<tr>
<td>Enalapril</td>
<td>Vasotec Vaseretic&lt;sup&gt;c&lt;/sup&gt; Lexxel&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Merck Merck AstraZeneca</td>
<td>12/24/85 10/31/86 12/27/96</td>
<td>2000 Q3</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>Prinivil Zestril&lt;sup&gt;a&lt;/sup&gt; Prinazide&lt;sup&gt;b&lt;/sup&gt; Zestoretic&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Merck AstraZeneca Merck AstraZeneca</td>
<td>12/29/87 05/19/88 02/16/89 02/20/00</td>
<td>2002 Q3</td>
</tr>
<tr>
<td>Ramipril</td>
<td>Altace</td>
<td>King</td>
<td>01/28/01</td>
<td>NA</td>
</tr>
<tr>
<td>Fosinopril</td>
<td>Monopril Monopril-HCT&lt;sup&gt;b&lt;/sup&gt;</td>
<td>BMS BMS</td>
<td>05/16/91 11/30/94</td>
<td>2003 Q4</td>
</tr>
<tr>
<td>Benazepril</td>
<td>Lotensin Lotensin-HCT&lt;sup&gt;b&lt;/sup&gt; Lorite&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Novartis Novartis Novartis</td>
<td>6/25/91 5/19/92 03/3/95</td>
<td>2004 Q1</td>
</tr>
<tr>
<td>Quinapril</td>
<td>Accupril Accuretic&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Pfizer Pfizer</td>
<td>11/19/91 12/28/99</td>
<td>2004 Q4</td>
</tr>
<tr>
<td>Perindopril</td>
<td>Aceon</td>
<td>Solvay</td>
<td>12/30/93</td>
<td>NA</td>
</tr>
<tr>
<td><strong>ARBs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Losartan</td>
<td>Cozaar Hyzaar&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Merck Merck</td>
<td>04/14/95 04/28/95</td>
<td>2010 Q2&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Valsartan</td>
<td>Diovan Diovan HCT&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Novartis Novartis</td>
<td>12/23/96 03/06/98</td>
<td>NA</td>
</tr>
<tr>
<td>Irbesartan</td>
<td>Avapro Avalide&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Sanofi-Aventis Sanofi-Aventis</td>
<td>08/20/97 08/30/97</td>
<td>NA</td>
</tr>
<tr>
<td>Eprosartan</td>
<td>Teveten Teveten HCT&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Abbott Abbott</td>
<td>12/22/97 11/01/01</td>
<td>NA</td>
</tr>
<tr>
<td>Candesartan</td>
<td>Atacand Atacand HCT&lt;sup&gt;b&lt;/sup&gt;</td>
<td>AstraZeneca AstraZeneca</td>
<td>06/04/98 09/05/00</td>
<td>NA</td>
</tr>
<tr>
<td>Telmisartan</td>
<td>Micardis Micardis HCT&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Boehringer Ingelheim Boehringer Ingelheim</td>
<td>11/10/98 11/17/00</td>
<td>NA</td>
</tr>
<tr>
<td>Olmesartan</td>
<td>Benicar Benicar HCT&lt;sup&gt;b&lt;/sup&gt; Azor&lt;sup&gt;e&lt;/sup&gt;</td>
<td>Sankyo Sankyo Sankyo</td>
<td>04/25/02 06/05/03 09/26/07</td>
<td>NA</td>
</tr>
</tbody>
</table>

<sup>a</sup>Approval dates found at: [http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm](http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm).<sup>b</sup>Contains hydrochlorothiazide.<sup>c</sup>Contains calcium channel blocker.<sup>d</sup>Generic losartan and losartan/hydrochlorothiazide were introduced in April 2010. ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; BMS = Bristol-Myers Squibb; FDA = U.S. Food and Drug Administration; HCT = hydrochlorothiazide; NA = not applicable.
Quarterly per-claim pharmacy reimbursement, as a proxy for drug price, was computed for all brand and generic ACE inhibitors and ARBs. Pharmacy reimbursements include the drug ingredient cost and dispensing fee but do not include manufacturer rebates (i.e., federally mandated rebates and supplemental state rebates have not been subtracted). All the data analyses were conducted using the SAS software package for Windows (Version 9.1.3, SAS Institute Inc., Cary, NC). Excel 2007 (Microsoft, Redmond, WA) was used to further develop the data.

Results

Table 2 shows prescription market shares for both the ACE inhibitor and ARB classes of drugs. Whereas ACE inhibitors had 100% of the Medicaid market in the number of claims from 1991-1994, their share fell to 64.7% by 2008. The share of brand drug prescriptions exceeded the share of generic prescriptions for ACE inhibitors through 2002. In 2003, this relationship reversed, and in 2008, 92.5% of Medicaid fee-for-service claims for ACE inhibitors were generic. All of the ARBs were still under patent and without generic competition at the end of the study period in 2008. Table 2 also shows payment market shares for the ACE inhibitors and ARBs. For the first time in 2007, and continuing in 2008, Medicaid spending on generic ACE inhibitors exceeded its spending on brand drugs in this class. Although brand drugs represented only 7.5% of the ACE inhibitor claims in 2008, they accounted for 32.1% of expenditures because their average price ($103.45) was almost 6 times the average generic ACE inhibitor price ($17.64; Table 3).

By 2005, the dollar market share for ARBs was higher than for ACE inhibitors and remained higher through 2008. In 2005, the ARBs accounted for 51.5% of Medicaid expenditures in the 2 drug classes rising to 65.1% in 2008.

The last 3 columns of Table 2 show the annual pharmacy payments (prices) per claim for the ACE inhibitors, ARBs, and for both drug classes combined. In 1991, an average pharmacy claim for an ACE inhibitor cost these Medicaid programs $37.24. In 2008, the average price per claim had fallen to $24.03. After adjusting both values by their year-appropriate consumer price index (CPI) values (136.2 and 215.3 base 1982-1984 for 1991 and 2008, respectively, for an inflation rate of 58.1%), Medicaid enjoyed a real price drop of 59.2% for ACE inhibitors in 2008 compared with 1991. In contrast, the average price of an ARB prescription rose from $38.24 in 1995 to $81.98 in 2008. After adjusting by the change in the CPI (from 152.4 in 1995 to 215.3 in 2008, for an inflation rate of 41.3%), the average ARB price rose in real terms by 51.7% from 1995 to 2008. Figure 2 shows the trends in average ACE inhibitor and average ARB prices along with the trend in the CPI over the same time period from 1991 to 2008.

In 2008, the Medicaid programs combined spent $309.8 million on ACE inhibitors and ARBs, with 64.7% of the claims for ACE inhibitors. At an average price per claim of $24.03, ACE inhibitors were significantly cheaper than the ARBs, which cost an average of $81.98 per claim. If the ACE inhibitor share had been reduced from 35.3% to 25.0%, an attainable goal, the average price per claim would have fallen from...
would have produced cost savings of $142.3 million (46%),

2008  6,959,548  $309,842,354  7.5%  92.5%  32.1%  67.9%  64.7%  35.3%  34.9%  65.1%  $24.03  $81.98  $44.52

2005  24,382,606  $1,000,142,045  20.6%  79.4%  50.0%  50.0%  67.7%  32.3%  54.0%  46.0%  $37.06  $61.36  $45.32

2004  25,052,642  $1,001,525,549  31.1%  68.9%  54.4%  45.6%  70.0%  30.0%  53.4%  46.6%  $30.48  $62.18  $39.98

2003  22,717,810  $898,430,207  45.6%  54.4%  61.3%  38.7%  72.0%  28.0%  58.4%  41.6%  $32.07  $58.78  $39.55

2002  19,866,643  $804,525,700  67.8%  32.2%  73.9%  26.1%  75.5%  24.5%  66.3%  33.7%  $35.59  $55.59  $40.50

2001  17,087,892  $678,945,950  74.9%  25.1%  77.1%  22.9%  78.6%  21.4%  71.3%  28.7%  $35.24  $48.37  $37.30

1999  10,417,985  $365,062,415  88.8%  11.2%  96.6%  3.4%  88.3%  11.7%  84.7%  15.3%  $33.60  $46.00  $35.04

1998  13,720,387  $530,752,819  96.5%  3.5%  96.9%  3.1%  100.0%  0.0%  100.0%  0.0%  $40.31  $44.52

1997  8,792,962  $312,588,794  78.4%  21.6%  87.5%  12.5%  92.9%  7.1%  91.3%  8.7%  $37.24  $44.52

1996  7,575,753  $296,581,719  82.1%  17.9%  85.5%  14.5%  98.1%  1.9%  98.0%  2.0%  $39.11  $41.10  $39.15

1995  7,600,760  $312,848,726  96.1%  3.9%  96.6%  3.4%  100.0%  0.0%  100.0%  0.0%  $41.17  $38.24  $41.16

1994  6,980,174  $281,378,322  97.3%  2.7%  97.8%  2.2%  100.0%  0.0%  100.0%  0.0%  $40.03  $40.03

1993  6,768,406  $270,943,988  99.0%  1.0%  99.2%  0.8%  100.0%  0.0%  100.0%  0.0%  $37.24  $37.24

1992  6,100,269  $236,948,154  99.9%  0.1%  100.0%  0.0%  100.0%  0.0%  100.0%  0.0%  $38.84  $38.84

1991  4,812,732  $179,228,516  100.0%  0.0%  100.0%  0.0%  100.0%  0.0%  100.0%  0.0%  $38.84

$44.52 to $38.52, and Medicaid program expenditures would have been $41.8 million less in 2008. The savings opportunity was $102.3 million in 2008 if the ACE inhibitor ratio had been 90%, with a reduction in the average price per claim from $44.52 to $29.83.

On top of these savings, there are some additional savings from a higher percentage of generic, versus brand, ACE inhibitor prescriptions. In 2008, there were 335,925 claims for brand ACE inhibitors at an average price of $103.45 per claim, compared with the $17.64 average for generic ACE inhibitor claims (Table 3). Multiplying the number of claims by the difference in price of $85.81 per claim means that there was an additional unrealized savings opportunity of $28.7 million if all ACE inhibitors were dispensed as generic in 2008.

The maximum savings opportunity in 2008, attainable through greater use of generic ACE inhibitors, was $75.1 million if all ACE inhibitors were dispensed as generic and 75% of the combined ACE inhibitors and ARBs were dispensed as ACE inhibitors; the average price per claim would have been $33.73 instead of $44.52. Even higher utilization of generic ACE inhibitors at 90% of the combined ACE inhibitors and ARBs would have produced cost savings of $142.3 million (46%), associated with a reduction in the average price per claim from $44.52 to $24.07.

By dividing total reimbursement by the number of claims,
Discussion

The $309.8 million in total Medicaid fee-for-service expenditures on ACE inhibitors and ARBs combined represented approximately 1.5% of total Medicaid spending of approximately $21.0 billion on outpatient prescription drugs (Figure 1). From 1991 to 2005, the year before the Medicaid-Medicare dual eligibles were moved to Medicare Part D, Medicaid’s spending on ACE inhibitors and ARBs rose from $179.2 million to over $1 billion (Table 2). There are several reasons for the 458% increase in spending on ACE inhibitors and ARBs. First, Medicaid enrollment has been increasing over time; in 1991, there were 28.3 million Medicaid beneficiaries, and by 2005, there were 45.4 million Medicaid beneficiaries, a 60% increase in enrollment over this 14-year period. In 2006, dual Medicaid-Medicare eligibles were transferred to Medicare Part D for their pharmacy benefit, resulting in a large drop in Medicaid spending for pharmaceuticals. However, the current economic recession that started in December 2007 brought significant job losses, loss of employer-offered health insurance, and a rise in the number of households requiring public assistance. Second, the prevalence of cardiovascular disease and diabetes has been rising in the United States. The age-adjusted hypertension prevalence over the period 1988 to 1994 was 24.4% among U.S. adults, rising to 28.9% during the

average per-claim prices can be determined for all of the individual ACE inhibitors and ARBs. All of the brand ACE inhibitors and ARBs have had rising prices over time. For example, the price of brand captopril (Capoten) rose from $40.94 in 1991 Q1 to $230.39 in 2008 Q4, representing a 462.8% increase, far exceeding the rate of inflation over this period. The price of brand enalapril (Vasotec) rose from $35.09 in 1991 Q1 to $118.36 in 2008 Q4. The price of brand benazepril went up from $84.60 in 2004 Q2 to $120.63 in 2008 Q4, representing a 42.6% increase in just 4.5 years. The price of brand valsartan (Diovan) rose by 97% from $44.38 in 1997 Q1 to $87.52 in 2008 Q4.

The average prices of generic captopril, enalapril, and lisinopril showed a steady decline after the entry of additional generic manufacturers. By 2008 Q4, the average price per claim was $9.93, $29.62, and $10.30 for captopril, enalapril, and lisinopril, respectively. The price of captopril decreased 85% from $55.30 in 1996 Q3 to $8.28 in 2005 Q4 as more and more captopril manufacturers entered the market and as the Medicaid programs were able to capture these savings through their reimbursement policies. Table 3 shows average prices for brand and generics for each of the ACE inhibitors and ARBs in 2008. Average reimbursement per claim was higher for several of the brand ACE inhibitors than for the ARBs, but the volumes were, of course, smaller (data not shown).
The age-adjusted (child plus adult) diabetes prevalence nearly doubled from 3.0% in 1991 to 5.7% in 2007. Third, the mortality rate for cardiovascular disease has decreased over time; hence, individuals are now taking ACE inhibitors and ARBs, chronic heart medications, for longer periods. Since 1968, cardiovascular disease death rates have fallen in the United States, including a 4.0% average annual decline in the age-adjusted mortality rate from cardiovascular diseases from 1999 to 2006. Finally, clinical guidelines and clinical trial results have encouraged increased prescribing of ACE inhibitors and ARBs.

Therefore, the increase in Medicaid spending on ACE inhibitors and ARBs is primarily attributable to increased utilization and not to price increases, although brand prices rose throughout the period. As shown in the last column of Table 2, the average price per claim rose from $37.24 in 1991 to $41.02 in 2005, representing just a 10% increase.

The rise in utilization of these drugs is probably not due to combination therapy with ARBs and ACE inhibitors because combination therapy with these 2 drugs is not encouraged in the United States. The Val-HeFT (Valsartan Heart Failure Trial) study showed beneficial effects on the combined endpoint of morbidity and mortality in patients who received an ARB in addition to ACE-inhibitor therapy, but subgroup analysis showed deleterious effects on morbidity and mortality when an ARB was given to patients receiving background therapy consisting of an ACE inhibitor plus a beta-blocker. Moreover, the ONTARGET study suggested that although the combination therapy can cause further reduction of albuminuria relative to ACE inhibitor or ARB monotherapy, the combination therapy had an adverse effect on renal function. In summarizing the results of the 4 trials devoted to ACE inhibitor and ARB combination therapy, McMurray (2008) concluded that the addition of an ARB to an ACE inhibitor had no benefit and increased the number of adverse events in patients with arterial disease. For patients with heart failure, however, the addition of an ARB might be beneficial. Generally, in the United States, hypertensive patients take either an ACE inhibitor or ARB but not both.

The influences on spending already discussed are largely beyond the control of state Medicaid programs. However, there are 2 Medicaid policies that can have a major impact on spending in these drug classes. First, most state Medicaid programs either require or strongly encourage the use of generic drugs when they become available following patent expiration of their brand counterparts. In 2008, 92.5% of Medicaid fee-for-service ACE inhibitor pharmacy claims were for generics. However, since the average price per brand ACE inhibitor claim was $103.45 compared with an average generic price per claim of $17.64, the Medicaid state programs together could have saved $28.7 million (for 335,925 brand ACE inhibitor claims) if they had reimbursed for generic claims only in 2008. Second, greater use of ACE inhibitors relative to ARBs would have produced large savings, but this cost outcome would have required interventions such as PA or step-therapy for the ARBs.

Since ACE inhibitors are well tolerated, the step-up approach from ACE inhibitors to ARBs is promising for reducing Medicaid spending. According to our analysis, Medicaid fee-for-service programs could have saved between $41.8 million and $102.3 million with PA for ARBs in 2008, depending on the assumptions made about the ratio of utilization of ARBs. Research reported in this journal by Yokoyama et al. found significant cost savings associated with step-therapy for ARBs implemented in May 2001 in 3 health plans with approximately 1 million members. The proportion of ACE inhibitor or ARB patients who received an ARB was reduced from 31% to 18% in the 12 months following the intervention, producing $368,000 in annual savings or $0.03 per member per month (PMPM). An accompanying editorial pointed out that the cost savings were actually $0.06 PMPM if the step-therapy intervention had been followed for a full year, closer to the cost savings of $0.11 PMPM reported by Gleason et al. for an ARB step-therapy intervention that was implemented in 2006. Although some state Medicaid programs such as Massachusetts, Washington, Maine, and Indiana have a PA requirement, not all do. Fischer et al. (2007), compared Medicaid expenditures for states with a PA requirement versus those without and found that step-therapy did indeed reduce ARB use and provided a method to significantly reduce Medicaid spending on antihypertensives.

**Limitations**

First among the limitations is the potential invalidity of the Medicaid national database. When we summed all Medicaid fee-for-service claims in 2008 in the national database, we found that Medicaid had a total of $24.3 billion in expenditures on all outpatient prescription drugs. This number compares with the $21.0 billion National Health Expenditure figure upon which Figure 1 is based, but the $21 billion figure apparently includes spending on Medicaid beneficiaries in managed care as well as fee-for-service. Some of the higher cost in the national database of fee-for-service claims is explained by pharmacy reimbursement prior to subtraction of drug manufacturer rebates. However, the proportion of total Medicaid beneficiaries has risen significantly, from only 9.5% in 1991 to 40.1% in 1996 and 70.9% in 2008. We did not determine the extent to which the national Medicaid fee-for-service database that we used includes managed Medicaid pharmacy benefits that are carved out of managed care.

Second, we discovered apparent errors in the national fee-for-service database for 5 calendar quarters from the inception of Medicare Part D program in January 2006 through the first quarter of 2007, necessitating our recalculation of expenditures...
to match the claims volume for ARBs and ACE inhibitors. However, these data manipulations did not affect our primary cost savings calculations, which were based on claims data in 2008.

A third limitation of this research is the inability to consider the effects of drug manufacturer rebates in reducing the net cost to the Medicaid programs. The Medicaid Drug Rebate Program, established by the Omnibus Budget Reconciliation Act of 1990, requires a drug manufacturer to enter into and have in effect a national rebate agreement with the secretary of the Department of Health and Human Services in order for states to receive federal funding for outpatient drugs dispensed to Medicaid patients. Rebate percentages are based on average manufacturer prices, and the percentage is higher for innovator drugs than for noninnovator (generic) drugs.55 In addition, a number of states have been collecting state-only supplemental rebates in conjunction with a preferred drug list.13 Therefore, the claims data that we used in the present study overstate the actual net drug acquisition cost to the Medicaid programs by ignoring rebates and do not include the managed Medicaid pharmacy claims that are not part of the federally administered Medicaid Drug Rebate Program.

Conclusions

In 2008, state Medicaid programs spent $309.8 million on ACE inhibitors and ARBs. Although many factors explaining this expense by affecting utilization (e.g., prevalence of hypertension, heart disease, and diabetes) are beyond the control of program administrators, cost savings can be obtained through a higher percentage of generic drug prescriptions and a higher percentage of ACE inhibitors in the total of ACE inhibitor and ARB utilization. In 2008, Medicaid could have saved up to $28.7 million (9%) through 100% utilization of generic ACE inhibitors and up to $142.3 million from 90% utilization of ACE inhibitors in the combined class of ARBs and ACE inhibitors.

DISCLOSURES

Guo reported consultant relationships with pharmaceutical manufacturers with brand drugs in the class of ACE inhibitors and ARBs, including Novartis, AstraZeneca, and Bristol-Myers Squibb. The other 3 authors reported no financial or other potential conflicts of interest related to the subject of this manuscript. A preliminary version of this study was presented as an unpublished poster at the 15th Annual Meeting of the International Society for Pharmacoeconomics and Outcomes Research in Atlanta, Georgia, in May 2010.

All 4 authors contributed to the study concept and design. Bian collected the data with the assistance of Guo. Bian and Kelton interpreted the data and wrote and revised the manuscript with the assistance of Guo and Wigle.

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REFERENCES


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Evaluation of Health Plan Member Use of an Online Prescription Drug Price Comparison Tool

Norman V. Carroll, PhD; Matthew P. Mitchell, PharmD, MBA; H. Eric Cannon, PharmD; Bryan W. York, BS, CPA; and Robert S. Oscar, BS Pharm

ABSTRACT

BACKGROUND: Health plans have implemented tiered copayment systems to incentivize members to use less expensive medications. However, members need drug price information to make comparisons among therapeutic alternatives. Many health plans and pharmacy benefit management companies have implemented online prescription drug price comparison tools to provide such information. There has been little published evaluation of these tools.

OBJECTIVE: To evaluate use of an online price comparison tool—MyPharmacyTools (MPT)—by the measures of (a) the extent to which the tool was used, (b) changes in use over the first year after implementation, and (c) the types of members who were most likely to use the tool.

METHODS: Data were provided by a 500,000-member integrated health plan with approximately 156,250 enrolled families. The sample included only families with continuous eligibility for all members from July 1, 2006, through June 30, 2008; use of 1 of 7 common copayment structures; and use of the pharmacy benefit in every quarter of the study period. Data collected on each member, using pharmacy claims for the time period July 1, 2007, through June 30, 2008, included annual drug costs (total, out-of-pocket, plan-paid, and mail order) and number of unique drugs and unique generic drugs taken during the third quarter of 2007. Data collected also included whether the member had each of several selected chronic diseases (as inferred from drug claims for the third quarter of 2007) and demographics. Age, gender, and family size were taken from eligibility files. Other demographic data were imputed to members from the demographics of the ZIP code in which they resided. MPT was made available to members on July 1, 2007. Use of MPT was measured as the number of times members logged into the site for each quarter during the subsequent year. Statistical analyses were conducted at the family rather than at the individual level, and families were defined as users if any family member used MPT at least once during the year. Between-group comparisons were evaluated with t-tests, Pearson chi-square tests, and analyses of variance.

RESULTS: Data were analyzed for 8,909 families composed of 28,537 health plan members, of which 464 (5.2%) families used MPT at least once between July 2007 and June 2008. A total of 141 families used MPT in the first quarter it was available, 170 families used it in the second quarter, 185 families in the third quarter, and 182 families during the fourth quarter. Users had significantly higher mean total drug costs ($4,477 [$9,647] vs. $2,848 [$3,473], P<0.001) and generic drugs ($9,647] vs. $2,848 [3,473], P<0.001) and cardiovascular disease (P=0.013), and used drugs for a greater number of chronic diseases (P=0.049), compared with less frequent MPT users.

CONCLUSIONS: About 5% of families in a sample from a large integrated health plan used an online prescription drug cost comparison tool during the first year it was available. Use increased over the year. Users were more likely to have several chronic diseases, took more prescription drugs, and had higher drug costs than nonusers. Further, users with more chronic diseases and more prescriptions were more likely to use the tool consistently throughout the year. These results indicate that the tool was successful in reaching health plan members who could most benefit from comparative prescription drug price information.

What is already known about this subject

• Spending on prescription drugs in noninstitutional settings in the United States increased from $12 billion in 1980 to $234 billion in 2008.
• Use of generic and therapeutic alternatives rather than more expensive brand or nonpreferred formulary medications generates substantial savings for both health plans and members.
• Health plan members need convenient, benefit-specific comparative drug pricing information in order to make cost-effective prescription drug choices. This information would allow members to determine the therapeutic and generic alternatives to the medicines they are currently taking, see their copayments and the cost to the health plan for both their medicines and alternatives, and compare prices for 30- and 90-day supplies.
• Many health plans attempt to provide such information through online prescription drug price comparison tools.

What this study adds

• This is the first published study to evaluate use of an online prescription drug cost comparison tool.
• In a sample of 8,909 families with similar prescription drug copayment structures, continuous enrollment for 2 years, and use of the pharmacy benefit in every quarter for 2 years, 464 (5.2%) used an online prescription drug price comparison tool during the first year it was available in a 500,000-member, 156,250-family integrated health plan.
S

pending on prescription drugs in noninstitutional settings has been rising steadily for many years. Spending in the United States increased from $12 billion in 1980 to $234 billion in 2008.1 While the rate of growth has declined in recent years, the dollar amounts spent have continued to climb.1 One reason for the constant and continued increase in prescription spending is that health plan members are shielded from prescription prices by insurance coverage. The prices that insured consumers (i.e., health plan members) pay out-of-pocket for prescription drugs, in the form of copayments and coinsurance, are far less than the actual costs of these products. Given that 90% of prescriptions dispensed in retail and mail order pharmacies are covered by some type of insurance, this is a significant problem.2

Tiered copayment benefit designs were implemented, at least in part, to address this problem by providing members with financial incentives to use products that have a lower net cost to the plan. If they choose to use more expensive products, they are required to pay at least part of the increased cost through higher copayments. Of commercial payers, 81% have a 3-tier copayment design.3 More recently, coinsurance has become a popular benefit for prescription plans. In a recent survey of commercial payers, only 47% used dollar copayments exclusively; the remaining 53% offered a combination of coinsurance and copayments.3 Coinsurance designs increase the need and demand for information on actual prices allowed by the plan. In order for members to take an active role in prescription selection, or at least have an awareness of prescription drug alternatives, they need convenient access to comparative prescription price information. This need is especially important for members with chronic diseases and high drug costs. These members have the most to gain personally and could have the biggest impact on the health plan’s drug costs by switching to lower-cost alternatives.

Physicians are a potential source of comparative price information for consumers. However, a number of studies have indicated that members cannot rely on physicians to provide accurate drug price information. A 2007 review by Allan et al. indicated that physicians consistently overestimated the costs of inexpensive drugs, underestimated the cost of expensive drugs, estimated drug costs within 20%-25% of actual costs only 31% of the time, and reported needing more drug cost information than was available to them.4 In a 2007 survey of internists, family practitioners, and general practitioners in Hawaii, Tseng et al. found that despite use of health information technology (HIT) by approximately 80% of respondents, less than 20% reported knowing retail drug prices or copayments most or all of the time. The authors speculated that the generally “modest” association between HIT and knowledge of drug costs was due to lack of cost and price information in the HIT used.3 Two other studies indicated that when physicians use HIT with well-integrated cost information, they are less likely to prescribe expensive drugs.6,7

A number of states now offer online prescription price posting to provide consumers with better access to prescription price information.8 Most of these sites base posted prices on the usual and customary prices that pharmacies report on Medicaid claims. As a result, little information is available for pharmacies or drug products with low Medicaid volume. A study of state prescription drug web sites concluded that the posted information was neither timely nor comprehensive.8 Also, the prices reported provide little assistance to consumers with prescription drug coverage who need information on plan-specific prices.

In order to give members access to cost-effective medication options many health plans, pharmacy benefit management companies (PBMs), and other organizations have implemented online prescription drug price comparison tools. A recent article in the trade press indicates increasing consumer demand for such tools.9 The available tools represent a range of individualization and precision. The less sophisticated price comparison tools provide “average” retail prices that are based on surveys of pharmacy prices or billed amounts. Tools that are not sponsored by health plans, such as those found on DestinationRx,10 Rxexaminer,11 or Consumer Reports,12 base their prices on surveys of pharmacy prices. Tools posted by health plans are more likely to base their prices on billed or allowed charges across the plan. As examples, RegenceRx (Portland, OR)13 and SelectHealth (Salt Lake City, UT)14 offer price comparison tools that are available to both members and nonmembers. A screenshot of SelectHealth’s public price lookup web page is shown in Figure 1.

The more sophisticated tools provide individualized, benefit-specific information. That is, based on the member’s specific plan and benefit design information, these tools indicate what the member would pay out-of-pocket for a given product, identify the product’s therapeutic and generic alternatives, compare pricing for 30-day and 90-day supplies, and indicate the member’s financial responsibility for each of the

What this study adds (continued)

• Families that used the tool had higher mean [SD] total drug costs ($4,477 [89,647] vs. $2,848 [3,473]), used significantly more unique drug products (7.7 [5.7] vs. 5.9 [4.5]), and were more likely to use medications for behavioral health problems, hypercholesterolemia, gastric disorders, diabetes, epilepsy, asthma, and cardiovascular diseases than nonusers of the tool.
• Among users, families that used the tool in more quarters of the year had a greater number of chronic diseases (as defined by the proxy of drug utilization), took a greater number of unique drugs and unique generic drugs, and had higher out-of-pocket and mail order drug costs compared with less frequent users.

• Families that used the tool had higher mean [SD] total drug costs ($4,477 [89,647] vs. $2,848 [3,473]), used significantly more unique drug products (7.7 [5.7] vs. 5.9 [4.5]), and were more likely to use medications for behavioral health problems, hypercholesterolemia, gastric disorders, diabetes, epilepsy, asthma, and cardiovascular diseases than nonusers of the tool.
• Among users, families that used the tool in more quarters of the year had a greater number of chronic diseases (as defined by the proxy of drug utilization), took a greater number of unique drugs and unique generic drugs, and had higher out-of-pocket and mail order drug costs compared with less frequent users.
**FIGURE 1** SelectHealth's Publicly Available Price Lookup Page

### Drug Lookup Results

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>FLOMAX 0.4 MG CAPSULE</th>
<th>Prostatic Hypertrophy Agent - alpha-1-Adrenoceptor Antagonists</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug Class</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Selected Quantity</td>
<td>30</td>
<td>Change Quantity Here 22-&gt;30</td>
</tr>
<tr>
<td>Maximum Days Supply</td>
<td>30 (Retail), 90 (Maintenance)</td>
<td></td>
</tr>
</tbody>
</table>

**Attention:** Prices are calculated based on QUANTITY. You may need to change the quantity in order to display the proper price. You may receive the greatest saving when ordering a 90-day supply using your maintenance benefit.

The information appearing below is intended to be a general guide to prescription drug costs and their alternatives. Due to the fluctuation of prescription drug costs, the estimates shown can vary and do not reflect the exact cost you will pay at the pharmacy. Displayed drugs and their costs do not constitute verification of coverage. Please refer to your Membership Guide and/or the Member Payment Summary specific to your group for more detail.

Please print this page and share the information with your Doctor. Please be aware that some of these therapeutic alternatives MAY NOT be appropriate for you. Also, dosages for the alternatives listed below may not be equivalent; varying from one drug to another.

View Printer Friendly

The copays reflected below are after any applicable deductibles have been met. The copays are not reflective of the difference in cost should you choose a brand when a generic is available.

**Please Make selection**

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Drug Cost</th>
<th>Product Status</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>FLOMAX 0.4 MG CAPSULE</em></td>
<td>$124.33</td>
<td>Tier 3</td>
</tr>
<tr>
<td>GEN TAMSULOSIN HCL 0.4 MG CAPSULE</td>
<td>$15.00</td>
<td>Tier 1</td>
</tr>
<tr>
<td>UROVATRAL 10 MG TABLET</td>
<td>$111.18</td>
<td>Tier 3</td>
</tr>
<tr>
<td>RAPPFLG 4 MG CAPSULE</td>
<td>$111.19</td>
<td>Tier 3</td>
</tr>
<tr>
<td>RAPPFLG 8 MG CAPSULE</td>
<td>$111.19</td>
<td>Tier 3</td>
</tr>
</tbody>
</table>

This information is designed to facilitate communication between you and your doctor. While the drugs in this list can be alternatives for one another, your specific dosage requirements must be determined by your doctor. RxEOB.COM is not recommending that you change your medication therapy.

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Note: Information based on available data; SelectHealth does not guarantee or warrant its accuracy.
alternatives. Due to the complexities of third-party prescription pricing, members may benefit from the use of more sophisticated tools. For example, what the member pays out-of-pocket for a given drug can vary with the type of drug (generic vs. brand), the formulary tier to which the drug is assigned, and whether the plan requires member copayments or coinsurance. Further, many of these variables change over time: brand drugs go off patent, tier status changes as a result of new clinical data and/or contracts, and copayments/coinsurance may change. As a result, members need sophisticated, benefit-specific tools to determine the prices they will ultimately pay for their medicines.

Although a number of health plans and PBMs have implemented online cost comparison tools, there is little published quantitative research evaluating the use of these price tools. The purpose of this project was to examine use of a more sophisticated price comparison tool in a large health plan. The specific objectives of the study were to determine the extent to which the tool was used in the first year after its implementation, to examine changes in use over the first year, and to identify the

![FIGURE 2 MyPharmacyTools Drug History Page](image-url)
types of members who were most likely to use the tool. The price comparison tool that we examined is branded as MyPharmacyTools (MPT) by the health plan evaluated in this study. The tool was developed and marketed by RxEOB, a health care technology company based in Richmond, Virginia, under the registered trademark of MyDrugBenefit. MPT includes a number of features. Members can use the tool to access their prescription drug history (Figure 2). This view includes a flashing dollar sign ($) icon that indicates the availability of less expensive alternatives. Clicking on this icon takes the member to a list of all generic and therapeutic alternatives for the product (Figure 3). Information shown on this page includes the member’s copayment or coinsurance amount, the billed amount (the sum of the amount paid by the health plan and the amount paid by the member for the product), and the tier status of the product and each of its alternatives. Further, the page shows this information for both 30-day retail and 90-day maintenance prescriptions. For this health plan, 90-day supplies can be obtained through either the mail order pharmacy or retail pharmacies participating in the 90-day retail program. The page also includes a warning that all products shown may not be appropriate for the member and that he or she should print the page and discuss it with his or her physician. Members can also use MPT to access drug monographs or to find clinical drug information from First DataBank’s National Drug Data File Plus (First DataBank, Inc., San Francisco, CA). The information in MPT is based on prescription claims, eligibility files, and drug benefit design information. As a result, the costs shown are member- and benefit-specific and indicate the amount the member will be responsible to pay at the point of service.

Methods

Data for the study were provided by SelectHealth, a 500,000-member integrated health plan located in intermountain western United States. SelectHealth offers only commercial health plans. The plan does not use an external PBM; these functions are handled internally. SelectHealth therefore has direct responsibility for managing the pharmacy benefit including controlling drug costs.

The selection of members for the study (Figure 4) was undertaken by first searching all pharmacy claims with dates of service from July 1, 2006, through June 30, 2008, and identifying the benefit type for each claim. We then identified the 20 benefit types accounting for the largest number of pharmacy claims. From these, we selected 7 benefit types with similar design; all 7 had a 3-tier benefit. The retail copayments for a 30-day supply ranged from $7/$20/$35 to $10/$30/$45 and the mail order copayments for a 90-day supply ranged from $10/$50/$90 to $10/$50/$90. Examples of excluded benefit types were retail copayments of $10/25%/50% and 20%/20%/30% with 90-day supply copayments of $10/25%/25% and $40/$80/$120, respectively. Because benefit type (e.g., low copayments versus high copayments or copayments versus coinsurance) could affect use of the price comparison tool, we wanted to ensure that all sampled members had similar benefit types.

From the 7 similar benefit types, we selected members who either had a claim, or had a family member with a claim, for every quarter in the study period. This was done to ensure that the sample included only continuously enrolled members. Using eligibility files for the most recent quarter, April through June 2008, we then discovered that there were members in the sample who had lost coverage over the study period. For example, a dependent aged 24 years would have been covered by the plan at the beginning of the study period, when he was aged 23 years, but not at the end of the study period. The enrollment files do not automatically drop family members from the file when they become ineligible for coverage. Families with a member who had lost coverage during the study period were then dropped from the sample. This method had the disadvantage of potentially excluding members who were continuously enrolled but did not have, or have a family member with, a pharmacy claim in every quarter. However, the method did ensure that all members in the sample had been continuously enrolled during the study period.

Data collected on each member included annual drug costs (member out-of-pocket, plan-paid, mail order, and total), number of unique drugs and unique generic drugs dispensed during the third quarter of 2007, member demographics, and number and type of certain chronic diseases. Drug cost and utilization data were taken from pharmacy claims for dates of service from July 1, 2007, through June 30, 2008. The number of unique drugs was calculated using First DataBank’s Generic Code Number Sequence Number (GCN_SEQNO). The number of unique generic drugs was calculated using Medi-Span’s Multi-Source Code indicator (Wolters Kluwer Health, Indianapolis, IN) in combination with the GCN_SEQNO. Age, gender, and family size were taken from eligibility files. Other demographic data were imputed to families as the demographics of the ZIP code in which they resided and included median household income and the proportion of residents having a high school education, a bachelor’s degree from college, married, below the Federal poverty line, and race (Latino, African-American or Caucasian). These data were based on the 2000 U.S Census and were found at http://zipskinny.com.

The diseases included in the study were behavioral problems, hypercholesterolemia, diabetes, gastric disorders, epilepsy, cardiovascular problems, and asthma. We included these diseases because they are common chronic conditions and because drugs are commonly used to treat them. For example, Druss et al. (2001) reported that 25% of the U.S. community-dwelling population had mood disorders, diabetes, heart disease, asthma, or hypertension. We included epilepsy and gastric disorders because of the high rate of use of drugs...
**Evaluation of Health Plan Member Use of an Online Prescription Drug Price Comparison Tool**

**FIGURE 3** 
MyPharmacyTools Drug Lookup Results Page

---

**Drug Lookup Results**

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>FLOMAX 0.4 MG CAPSULE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug Class</td>
<td>Prostatic Hypertrophy Agent - alpha-1-Adrenoceptor Antagonists</td>
</tr>
<tr>
<td>Selected Quantity</td>
<td>30</td>
</tr>
<tr>
<td>Change Quantity Here 22-&gt;:</td>
<td>30</td>
</tr>
<tr>
<td>Maximum Days Supply</td>
<td>30 (Retail), 90 (Maintenance)</td>
</tr>
</tbody>
</table>

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### Please Make Selection

<table>
<thead>
<tr>
<th>Retail Pricing</th>
<th>Maintenance Pricing</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Retail Copay</th>
<th>Billed Amount</th>
<th>Product Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>FLOMAX 0.4 MG CAPSULE</td>
<td>$62.17</td>
<td>$124.33</td>
<td>Tier 3</td>
</tr>
<tr>
<td>TAMUSLIN HCL 0.4 MG CAPSULE</td>
<td>$10.00</td>
<td>$15.00</td>
<td>Tier 1</td>
</tr>
<tr>
<td>RAPFLO 0 MG CAPSULE</td>
<td>$55.59</td>
<td>$111.19</td>
<td>Tier 3</td>
</tr>
<tr>
<td>RAPFLO 0.5 MG CAPSULE</td>
<td>$55.59</td>
<td>$111.19</td>
<td>Tier 3</td>
</tr>
<tr>
<td>URCAFAR 10 MG TABLET</td>
<td>$55.59</td>
<td>$111.18</td>
<td>Tier 3</td>
</tr>
</tbody>
</table>

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to treat these conditions in our sample. The presence of each disease was imputed based on prescription drugs the member was taking during the third quarter (July through September) of 2007. Drugs were matched to diseases using First DataBank Enhanced Therapeutic Classification Codes (Table 1).

MPT was first made available to plan members on July 1, 2007. Members were informed of its availability through several quarterly newsletters distributed after implementation of the tool. Members from select large employers also received education about the tool from onsite health fairs and brown bag presentations. Members could also have received information about MPT from educational materials placed in physician offices and pharmacies in the form of tear pads. Use of MPT was measured as the number of times members logged onto the site (log-ins) for each quarter during the subsequent year. Each member had his or her own unique log-in identifier. Past research has indicated that the individuals who conduct online searches for health information are frequently doing so for other members of the family. As a result, we conducted statistical analyses at the family rather than the individual level. To do so, we summed the number of times MPT was accessed by any family member for each quarter. We also measured costs, utilization, disease presence, and demographics at the family level. This entailed summing all family members’ drug costs and utilization, defining presence of disease as whether any member of the family had the disease during the third quarter of 2007, and recording age and gender of the health plan subscriber for the family.

Families in the sample were categorized into 2 groups. Users were defined as families that had used MPT at least once during the year. Nonusers were defined as families that had not used the tool during the year. Drug costs and utilization, presence of chronic diseases, and demographics were compared between groups using t-tests and Pearson chi-square tests. T-tests for unequal variances were used for cost and utilization data.

Two analyses were performed. The first analysis used all prescription claims. The second analysis excluded claims for drugs used for acute conditions and for serious, high-cost conditions. Drugs for acute conditions were identified with the First DataBank Maintenance Drug Indicator (MAINT). Drugs for serious, high-cost conditions that were excluded were immunosuppressives, antiretrovirals, herpes agents, Hepatitis B treatments, antineoplastics, antineuasthenic agents, Alzheimer’s Disease treatments, Parkinson’s Disease treatments, and disease-modifying antirheumatic drugs (DMARDs). The second comparison was made because members have less opportunity to use MPT for acute conditions and because they may be less willing to switch drugs, and consequently to use MPT, for serious medical conditions. Further, for certain serious conditions, drugs that may be categorized as alternatives because they are in the same class (e.g. antineoplastics, human immunodeficiency virus [HIV] antivirals) may not be reasonable treatment options for the specific patients and conditions being treated.

We used Pearson chi-square and analysis of variance tests to examine the relationship between the consistency of use of MPT over the year—defined as the number of quarters in which MPT was used—and drug costs, drug use, and imputed disease prevalence. These analyses included only users of MPT. This research was approved by the Intermountain Health Care Office of Research and Institutional Review Board. All analyses were conducted using SAS version 9.2 (SAS Institute Inc., Cary, NC) and an a priori alpha of 0.05.

Results
Data were analyzed for 28,537 members from 8,909 families (Figure 4). Of these, 464 (5.2%) families used MPT at some time during the year. Approximately 147,081 of 156,250 families were initially excluded from the sample either because they

![FIGURE 4 Sample Selection for Study](image-url)
TABLE 1  First DataBank Enhanced Therapeutic Classification Codes Used to Create Disease Categories

<table>
<thead>
<tr>
<th>Disease Category</th>
<th>Drug Type</th>
<th>First DataBank Enhanced Therapeutic Classification Codes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Behavioral</td>
<td>Antidepressant</td>
<td>527, 530, 2586, 2587, 2589, 2811, 2812</td>
</tr>
<tr>
<td></td>
<td>Antipsychotic and antimanic agents</td>
<td>535, 536, 2591, 2592, 2596, 2598, 2600, 3707, 3709, 3961, 5682, 6126</td>
</tr>
<tr>
<td></td>
<td>Antianxiety agents</td>
<td>2539</td>
</tr>
<tr>
<td></td>
<td>Psychotherapeutics</td>
<td>530, 2816, 5760</td>
</tr>
<tr>
<td></td>
<td>CNS stimulants</td>
<td>550, 551, 561, 5695</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>Antihyperlipidemics</td>
<td>264, 268, 2247, 3265, 3466, 5678, 5783, 5784, 5845</td>
</tr>
<tr>
<td>Gastric disorders</td>
<td>Ulcer drugs</td>
<td>438, 443, 444, 445, 2547, 5923</td>
</tr>
<tr>
<td>diabetes</td>
<td>Antidietics</td>
<td>156, 157, 161, 163, 2578, 2581, 5662, 5880, 5887, 5906, 6086, 6087, 6089, 6090, 6092, 6094</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Anticonvulsants</td>
<td>625, 628, 630, 631, 2683, 2684, 2686, 2687, 6027, 6028, 6029, 6030, 6125</td>
</tr>
<tr>
<td>Cardiac problems</td>
<td>Antihypertensives</td>
<td>224, 225, 230, 238, 239, 242, 2718, 2722, 2730, 5659</td>
</tr>
<tr>
<td></td>
<td>Diuretics</td>
<td>249, 250, 253, 254, 2713, 5658, 6043</td>
</tr>
<tr>
<td></td>
<td>Beta blockers</td>
<td>214, 221, 2527, 2528, 2529, 2530</td>
</tr>
<tr>
<td></td>
<td>Antianginals</td>
<td>206</td>
</tr>
<tr>
<td></td>
<td>Calcium channel blockers</td>
<td>2534, 4609, 4610, 4611</td>
</tr>
<tr>
<td></td>
<td>Antiarrhythmics</td>
<td>218, 219, 220, 2734</td>
</tr>
<tr>
<td></td>
<td>Anticoagulants</td>
<td>806</td>
</tr>
<tr>
<td></td>
<td>Cardiotonics</td>
<td>203</td>
</tr>
<tr>
<td></td>
<td>Platelet aggregation inhibitors</td>
<td>822, 823, 824, 5795, 5796</td>
</tr>
</tbody>
</table>

CNS = central nervous system.

Discussion

The sample for the present study consisted of 8,909 families with similar prescription drug copayment structures, to have a female subscriber than were those who did not use the tool (39.7% for users vs. 49.0% for nonusers, Pearson chi-square = 15.1, P < 0.001). Otherwise, there were no statistically significant demographic differences between users and nonusers (Table 2).

There were statistically significant differences in drug costs and use and presence of diseases (Table 2). Users had substantially higher drug costs and received substantially more unique drug products and unique generic drug products than did nonusers. These differences were found in both the analysis using all prescription claims and in the analysis that excluded claims for acute drugs and drugs for serious, high-cost diseases (data not shown). MPT users were significantly more likely to use drugs for each of the chronic diseases.

As shown in Table 3, more consistent users of MPT (i.e., those with use in more quarters of the year) had higher drug costs and drug use than did less consistent users. This trend was statistically significant for out-of-pocket drug costs, mail order drug costs, and total number of unique drugs and unique generic drugs received. Families that used MPT more consistently were more likely to use drugs for cardiovascular disease and diabetes (data not shown) and to use drugs for a higher number of chronic diseases (Table 3). The results shown in Table 3 are based on an analysis of the sample that included all drugs received.

had plans with benefit designs unlike those selected for the sample (as explained in the Methods section) or because the family did not have a prescription filled in each quarter of the July 2006 through June 2008 period. An additional 260 families were dropped because they included 1 or more members who became ineligible for coverage during the study period. Usage of MPT grew from 141 families in the first quarter the tool was available (July through September 2007) to 170 families in the second quarter, 185 families in the third quarter, and 182 families during the last quarter of the study period.

The typical subscriber in the study sample had a mean (standard deviation [SD]) age of 50.1 (11.4) years, was married, Caucasian, and lived in a ZIP code that had a median household income of $51,875 (Table 2). There were 3.2 (1.8) covered members in the typical subscriber's family. The typical family had mean annual total drug costs of $2,933 (4,050), took 6.0 (4.6) unique drugs, and 3.9 (3.2) unique generic drugs.

A total of 314 families (67.7% of users) used the tool during only 1 quarter of the year, 98 (21.1%) used it during 2 quarters, 40 (8.6%) families used it during 3 quarters, and 12 (2.6%) used it in each of the 4 quarters. Among users, the mean [SD] number of uses per family was 29.8 (55.3). The median was 13 uses during the year. The number of uses ranged from 2 to 617 per family during the year. Families that used MPT in more quarters of the year also had higher mean uses of the tool. Families that used MPT in only 1 quarter had mean [SD] uses of 14.0 (19.0); the means [SD] for families using the tool in 2, 3, and 4 quarters were 39.2 (42.5), 102.5 (105.3), and 123.4 (162.5), respectively. Families that used MPT were less likely
continuous enrollment for 2 years, and use of the pharmacy benefit in every quarter for 2 years, who were selected from a 500,000-member, 156,250-family integrated health plan. About 5% of families in this sample used an online prescription drug price comparison tool during the first year it was available. Use of the tool increased over the course of the year.

Users experienced substantially higher drug costs, received more prescription drugs, and were more likely to use drugs for a number of chronic diseases than nonusers. Further, users with higher drug utilization and more diseases used the tool more consistently over the course of the year.

A usage rate of 5% is consistent with documented rates of

<table>
<thead>
<tr>
<th>Pharmacy Claims Utilization and Cost</th>
<th>Full Sample n = 8,909</th>
<th>Families with No MPT Use n = 8,445</th>
<th>Families with Any MPT Use n = 464</th>
<th>P Valueb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total drug costsc</td>
<td>$2,933 [450]</td>
<td>$2,848 [3,473]</td>
<td>$4,477 [9,674]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Out-of-pocket drug costsd</td>
<td>$695 [612]</td>
<td>$685 [607]</td>
<td>$876 [669]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Plan paid drug costsc</td>
<td>$2,238 [5,635]</td>
<td>$2,163 [3,018]</td>
<td>$3,601 [9,285]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mail order drug costsf</td>
<td>$990 [1,886]</td>
<td>$951 [1,839]</td>
<td>$1,698 [2,508]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total number of unique drugsg</td>
<td>6.0 [4.6]</td>
<td>5.9 [4.5]</td>
<td>7.7 [5.7]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total number of unique generic drugsf</td>
<td>3.8 [3.2]</td>
<td>3.9 [3.2]</td>
<td>5.0 [3.9]</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Health Plan Enrollment Data</th>
<th>Mean [SD] or n (%)</th>
<th>Mean [SD] or n (%)</th>
<th>Mean [SD] or n (%)</th>
<th>P Valueb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of health plan members</td>
<td>3.2 [1.8]</td>
<td>3.2 [1.8]</td>
<td>3.3 [1.8]</td>
<td>0.465</td>
</tr>
<tr>
<td>in household mean [SD]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female subscribers n (%)</td>
<td>4,324 (48.5)</td>
<td>4,140 (49.0)</td>
<td>184 (39.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ZIP Code Information</td>
<td>Mean [SD]</td>
<td>Mean [SD]</td>
<td>Mean [SD]</td>
<td></td>
</tr>
<tr>
<td>Median household income</td>
<td>$51,875 [$12,296]</td>
<td>$51,842 [$12,287]</td>
<td>$52,425 [$12,439]</td>
<td>0.332</td>
</tr>
<tr>
<td>Percentage of high school graduates</td>
<td>89.1 [6.5]</td>
<td>89.1 [6.5]</td>
<td>89.2 [7.7]</td>
<td>0.849</td>
</tr>
<tr>
<td>Percentage married</td>
<td>61.2 [6.3]</td>
<td>61.2 [6.3]</td>
<td>60.9 [6.1]</td>
<td>0.340</td>
</tr>
<tr>
<td>Percentage below federal poverty line</td>
<td>6.9 [4.9]</td>
<td>6.9 [4.9]</td>
<td>6.8 [4.8]</td>
<td>0.589</td>
</tr>
<tr>
<td>Percentage Caucasian</td>
<td>87.1 [8.9]</td>
<td>87.1 [8.9]</td>
<td>87.0 [9.0]</td>
<td>0.777</td>
</tr>
<tr>
<td>Percentage African-American</td>
<td>0.7 [0.9]</td>
<td>0.7 [0.9]</td>
<td>0.7 [0.7]</td>
<td>0.734</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Diseases Imputed from Pharmacy Claims</th>
<th>n (%)</th>
<th>n (%)</th>
<th>n (%)</th>
<th>P Valueb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Behavioral diseases</td>
<td>3,569 (40.1)</td>
<td>3,351 (39.7)</td>
<td>218 (47.0)</td>
<td>0.002</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>2,450 (27.5)</td>
<td>2,284 (27.0)</td>
<td>166 (35.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gastric disorders</td>
<td>2,094 (23.5)</td>
<td>1,942 (23.0)</td>
<td>152 (32.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1,162 (13.0)</td>
<td>1,077 (12.8)</td>
<td>85 (18.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>990 (11.1)</td>
<td>892 (10.6)</td>
<td>98 (21.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>3,392 (38.1)</td>
<td>3,168 (37.5)</td>
<td>223 (48.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Asthma</td>
<td>967 (10.9)</td>
<td>902 (10.7)</td>
<td>65 (14.0)</td>
<td>0.025</td>
</tr>
</tbody>
</table>

*Demographics, with the exception of age and number of health plan members in the household, were measured as the demographics of the ZIP code in which the subscriber resided as taken from the 2000 U.S. Census. All demographic characteristics except median household income were measured as percentages of households in the ZIP code. The figures shown here are the mean [SD] of these percentages. Each family’s income was measured as the median household income of the ZIP code in which the family resided. The figure shown here is the mean [SD] of the median household incomes.

*Presence of disease was imputed based on drugs taken by family members. Drugs were matched to diseases using First DataBank’s Enhanced Therapeutic Classification Codes.

*Total drug costs were defined as the sum of drug costs paid by the member (out-of-pocket drug costs) and paid by the plan (plan-paid drug costs).

*Out-of-pocket drug costs were defined as the amount of drug costs paid by the member, including copayments, coinsurance, and deductibles.

*Plan-paid drug costs were defined as the amount of drug costs paid by the health plan, derived from the total allowed drug costs less the amount paid by members (out-of-pocket drug costs).

*Mail order drug costs were defined as the total cost of mail order drugs including both the plan-paid and member-paid amounts.

*The total number of unique drugs and total number of unique generic drugs were measured as of the third quarter of 2007 using First DataBank’s Generic Code Number Sequence Number (GCN_SEQNO). Drugs were defined as unique if they had the same chemical ingredients, strength, and route of administration. Drugs were defined as generic if they were coded as multisource (Y) by the Medi-Span Multisource Code generic drug indicator.

*MPT = MyPharmacyTools; SD = standard deviation.
response to similar types of communications. For example, response rates for direct mail (postcards and letters sent directly to consumers to solicit sales, contact information, or donations) average between 1% and 5%. Other web references indicate average “click through” rates of 6% or less for e-mail solicitations sent to large (i.e., more than 1,000-person) groups.25,26

The California Health Care Foundation (2006) commissioned a study of prescription drug, hospital, and physician cost comparison tools. The results indicated that 9% of respondents had compared information about 2 similar prescription drugs online, and 6% had looked for prescription prices online. Consumers with prescription drug insurance were less likely, and more educated and technologically savvy consumers were more likely, to search for prescription price information online.27

Ranganathan et al. (2009) sent U.S. mail and e-mail invitations to active and retired employees of General Electric to invite them to use a website providing physician-level quality data.28 A total of 5.8% of invitees registered to use the site. Fanjiang et al. (2007) sent letters to adult patients seeking a new primary care physician to invite them to view a website providing quality information about available primary care physicians.29 They sent an initial letter of invitation and a follow-up letter 2 weeks later. Seventeen percent of recipients responded to the letter by accessing the website. This response rate is substantially higher than the rate of use of MPT. An important difference between the studies is that patients in the study reported by Fanjiang et al. were targeted at the time they were making a decision about a primary care physician. Patients in our study were not specifically targeted at the time they were making decisions about prescription drug purchases. Fanjiang et al. commented that the rate of use in their study was higher than typically seen and that this finding was probably due to targeting patients at a time when the physician-specific quality information was particularly relevant to them.29

It should also be noted that use of MPT at the health plan we studied, according to plan administrators, was several times greater than use of any other content on the plan’s web page. Also, the rate of use for the tool increased over the first year it was in operation. This finding may suggest that rates of use will continue to increase in later years as plan members become more aware of the availability of the site and of its utility. A recent press release from AISHealth.com notes anecdotal reports of increased use of price comparison tools during the same time period as covered in this study.9

The results showed that those most in need of price information were more likely to use the site and that those with greater need used the site more consistently. Families that used drugs to treat more chronic diseases and that had higher drug use and costs were more likely to use the tool, and to use it more consistently, than were families with lower drug expenses
and fewer chronic diseases. This finding indicates that MPT is an effective vehicle for communicating comparative price information to a health plan’s sickest and highest drug cost members. In general, members with higher drug costs are older. Past research has indicated that older consumers are less likely to use the Internet or to search for health information online than younger consumers. As a result, we had initially suspected that health plan members with higher drug costs would not use MPT as frequently because of their age. However, our analysis indicated no age differences between users and nonusers but significant differences in drug costs and disease prevalence. This finding may be a result of analyzing data at the family level; older members may use younger relatives to do their searches. Or it is possible that high drug expenses provide the motivation that some older members need to induce them to use the Internet. It is also possible that the more Internet-experienced elderly used the site, while less experienced elderly members did not. Two recent studies indicate that consumers who use the Internet to search for health information are more experienced online users than consumers who do not.

Our research suggests several areas for future research. First, how can use of online price comparison tools be increased? Although our research indicated that members with higher costs were more likely to use MPT, there were many members with high drug costs who did not use it. Our research was not able to identify the reasons for these differences in use. Nonusers may differ from users in terms of their willingness to use online tools, their access to the Internet, their general ability to use computers, or their access to friends or relatives who would do online searches for them. Or, despite high drug costs, nonusers may simply have been less involved in and less concerned about prescription drug costs.

Second, does use of price comparison tools increase members’ use of less expensive generic and therapeutic alternatives? One goal of the health plan is to provide prescription price information to members so they can make more informed decisions. An additional health plan goal is to reduce drug costs. Research is needed to measure the extent to which MPT, and similar price comparison tools, result in members lowering health plan drug costs through more cost-effective drug choices.

Third, is usage of a price comparison tool affected by the level of specificity of price information provided? As mentioned earlier, tools available to the general public provide only average retail prices, while those offered by health plans are more likely to offer member- and benefit-specific information. It would be useful to determine if the additional specificity of price information was associated with greater use by members.

Finally, are there ways to enhance price comparison tools so that they are more useful and accessible to health plan members? A number of enhancements are currently being made to MPT to increase its utility and accessibility. These include automated alerts to inform members of savings opportunities (e.g., new generic drugs or therapeutic alternatives) when they log on to the website, outbound communication capabilities that would send such alerts and other messages (e.g., compliance reminders) directly to consumers’ e-mail accounts or telephones, and smartphone applications that would allow members to access comparative price information at the point of prescribing. Research will be needed to measure the effectiveness of such enhancements on members’ use and choice of prescription drugs. It would also be interesting to study whether the prescription drug choices of members who use comparative price information at the point of prescribing affect physicians’ prescribing practices and whether any such influence spills over to prescribing for nonmembers.

Limitations
First, only 1 tool was examined in 1 health plan. Rates of use and types of members who use price comparison tools could differ for different kinds of tools (e.g., those that provide only average retail price information rather than benefit- and patient-specific price information), by the extent to which plans promote use of price comparison tools, and by the types of members enrolled in the plans.

Second, we were unable to capture online prescription tool use for individuals who did not log into MPT. The health plan offers a public site where an individual can look up a drug's copayment tier, therapeutic alternatives, and approximate cash prices. The public site does not provide member-specific information such as copayment or coinsurance amounts for the drug or its alternatives. Specific member use of this public website cannot be captured because members can access information from the public site without logging into either MPT or the public site. The availability of the public site may be another reason that measured use of MPT was low during the study period.

Third, much of the demographic data used in the study was imputed from the demographics of the ZIP code in which the family resided. These data were taken from the 2000 U.S. Census so they are relatively old. In addition, ZIP codes may not be demographically homogeneous and the geographic boundaries of a given ZIP code may change over time. A number of the ZIP codes in which members resided in 2008 did not exist at the time of the 2000 Census. These factors limited the accuracy of the demographic data used in the study. As a result, there may have been demographic differences between users and nonusers that this study was not able to detect.

Fourth, presence of disease was inferred from members’ drug history. As a result, members who had a disease, but did not receive drug treatment for it, would not have been identified. This problem could occur, for example, for members with elevated lipids who were controlled with diet and exercise or
for depressed members treated by counseling without drug therapy. However, prescription drugs are first-line therapy for most of the diseases we examined. Consequently, it seems likely that this limitation had little effect on our results. Imputing the presence of disease from drug data may have also led to overestimating the prevalence of the chronic diseases in our study. For example, a patient taking a beta-blocker for migraine prophylaxis would have been classified as having cardiovascular disease. Similarly, a patient taking an anticonvulsant for pain relief would have been classified as having epilepsy.

Finally, some use of MPT could have been for persons other than members of the health plan. For example, adult plan members may have used the site to search for lower cost alternatives for elderly parents experiencing the Medicare Part D coverage gap. Although MPT would not provide specific costs that nonmembers would pay, it would provide information on generic and therapeutic alternatives and relative costs for nonmembers. As a result, the usage that was measured in this study could overstate the number of uses of MPT that directly benefited the health plan.

Conclusions
This study examined the use of an online prescription drug cost comparison tool for the first year after it was made available. The results indicated that about 5% of families in our sample used the tool at some time during the year and that usage increased over the year. Users were significantly more likely to use drugs to treat several chronic diseases, took significantly more prescription drugs, and had significantly higher drug expenses than nonusers. Further, users who purchased more prescriptions and had more chronic diseases were more likely to use the tool consistently throughout the year. These results indicate that the tool was successful in reaching health plan members who could most benefit from comparative prescription drug price information.

DISCLOSURES
Carroll’s work on this project was part of a sabbatical at RxEOB that was jointly funded by RxEOB and Virginia Commonwealth University. Oscar is Chief Executive Officer and York is Chief Operating Officer at RxEOB, the company that developed and markets the online prescription comparison tool. Cannon and Mitchell are employees of the health plan at which the online prescription price comparison tool was evaluated.

Concept and design were performed primarily by Carroll, with the assistance of Mitchell and York. Data were collected by Cannon, Mitchell, Oscar, and York and interpreted primarily by Carroll with the assistance of York, Mitchell, and Oscar. The manuscript was written by Carroll, with the assistance of Cannon, Mitchell and York, and revised by Carroll, with the assistance of Mitchell and York.

ACKNOWLEDGEMENT
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REFERENCES

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ABSTRACT

BACKGROUND: Patients with bone metastasis secondary to prostate or breast cancer or multiple myeloma are predisposed to skeletal-related events (SREs), such as surgery or radiation to the bone, pathologic fracture, and spinal cord compression. Inpatient costs of these and other SREs represent an estimated 49%-59% of total costs related to SREs. However, information on payer costs for hospitalizations associated with SREs is limited, especially for costs associated with specific SREs by tumor type.

OBJECTIVE: To examine costs from a payer perspective for SRE-associated hospitalizations among patients with multiple myeloma or bone metastasis secondary to prostate or breast cancer.

METHODS: Patients with SRE hospitalizations were selected from the MarketScan commercial and Medicare databases (January 1, 2003, through June 30, 2009). Sampled patients had at least 2 medical claims with primary or secondary ICD-9-CM diagnosis codes for prostate cancer, breast cancer, or multiple myeloma and at least 1 subsequent hospitalization with principal diagnosis or procedure codes indicating bone surgery, pathologic fracture, or spinal cord compression. For patients with prostate cancer or breast cancer, a diagnosis code for bone metastasis was also required. If secondary diagnoses or procedure codes for SREs were present in the claim, they were used to more precisely identify the type of SRE for which the patient was treated, resulting in 3 mutually exclusive categories: spinal cord compression with or without pathologic fracture and/or surgery to the bone; pathologic fracture with or without surgery to the bone; and only surgery to the bone. Related readmissions within 30 days of a previous SRE-associated hospitalization date of discharge were excluded to minimize the risk of underestimating costs. Mean health plan payments per hospitalization, measured as net reimbursed amounts paid by the health plan to a hospital after subtracting patient copayments and deductibles, were analyzed by cancer type and type of SRE.

RESULTS: A total of 555 patients contributed 572 hospitalizations that met the study criteria for prostate cancer, 1,413 patients contributed 1,542 hospitalizations for breast cancer, and 1,361 patients contributed 1,495 hospitalizations for multiple myeloma. The mean age range was 61 to 72 years, and the mean length of stay per admission was 5.9 to 11.6 days across the 3 tumor types. The ranges of mean health plan payments per hospital admission across tumor types were $43,691-$59,854 for spinal cord compression, with or without pathologic fracture and/or surgery to the bone; $22,390-$26,936 for pathologic fracture without spinal cord compression, with or without surgery to the bone; and $31,016-$42,094 for surgery to the bone without pathologic fracture or spinal cord compression.

CONCLUSIONS: The inpatient costs associated with treating SREs are significant from a payer perspective. Our study used a systematic process for patient selection and mutually exclusive categorization by SRE type and provides a per episode estimate of the inpatient financial impact of cancer-related SREs assessed in this study from a third-party payer perspective.

What is already known about this subject

- Two published studies have estimated the mean health care costs associated with treatment of skeletal-related events (SRE) in patients with cancer and bone metastasis, providing a broad picture of estimated costs in both the inpatient and outpatient settings.
- A study by Lage et al. (2008) of patients with prostate cancer estimated that the mean cost of SREs per person, measured as dollars billed to health plans, was $12,469 in 2006 dollars for treatment of pathologic fracture, spinal cord compression, surgery to bone, and radiation to bone in the year after initial SRE diagnosis.
- Delea et al. (2006) studied patients with breast cancer and estimated an average per SRE treatment cost over 60 months (mean follow-up 13.8 months) of $13,940 in 2002 dollars for pathologic fracture, spinal cord compression, radiation or surgery to bone, hypercalcemia, or use of opioid analgesics.
- In both studies, 49% or more of the health care costs were incurred in the inpatient setting, but the breakdown of inpatient costs by type of SRE was not provided. These studies report costs over time rather than costs per SRE episode. The majority of patients in both studies experienced only 1 SRE (78% in the prostate cancer study and 61% in the breast cancer study).

What this study adds

- The current study reports costs for inpatient treatment of SREs from the payer perspective, measured as net payment to the facility after subtracting patient copayments and deductibles, by type of SRE across 3 tumor types: prostate cancer, breast cancer, and multiple myeloma.
- Mean inpatient cost estimates for the 3 tumor types ranged from $31,016 to $42,094 for bone surgery; from $22,390 to $26,936 for pathologic fracture, and from $43,691 to $59,854 for spinal cord compression.
Bone is a common site for the spread of several malignancies as its nutrient-rich environment provides a favorable soil for colonizing tumor cells. When tumor cells metastasize to bone, they are thought to secrete cytokines and growth factors that induce osteoblasts (bone-forming cells) to release the protein RANK ligand (RANKL). In turn, RANKL promotes the formation and survival of osteoclasts (bone-resorbing cells), which, when activated, cause local bone destruction in the direct area of the tumor metastasis. Key growth factors are released from the bone breakdown that may promote proliferation, metastasis, and survival of tumor cells. Thus, a “vicious cycle” of tumor expansion and bone destruction resorption is perpetuated. Bone metastases can result in significant skeletal complications known as skeletal-related events (SREs), such as pathologic fracture, spinal cord compression, or need for surgery or radiation to bone. Nearly 70% of patients with metastatic prostate or breast cancer experience metastases to the bone, and up to 95% of patients with multiple myeloma experience osteolytic bone lesions, which may lead to SREs.

Breast and prostate cancers are the most prevalent cancers in the United States, with 1 in 8 women developing breast cancer and 1 in 6 men developing prostate cancer during their lifetimes. Additionally, virtually all cases of myeloma involve bone destruction. Given these facts, the economic burden that SREs associated with these cancers can place on health systems may be substantial. Treatments that can reduce or prevent SREs may reduce the economic burden of these skeletal complications. Intravenous bisphosphonates, primarily zoledronic acid (Zometa; Novartis), are effective for preventing SREs. Denosumab (Amgen), a RANKL inhibitor, has effectively delayed and reduced the occurrence of SREs compared with zoledronic acid in ongoing clinical trials. To better assess the potential cost-offsets gained by these therapies, it can be helpful to understand the cost burden that each type of SRE places on the health care system.

Treatment of SREs occurs in both inpatient and outpatient settings. Inpatient treatment represented an estimated 49%-59% of total SRE costs in previous research. This analysis focuses on third-party payer costs for treating SRE episodes in the inpatient setting by type of SRE. Previously published cost-of-SRE studies do not identify the attributable costs of individual types of SREs. A study of patients with advanced prostate cancer conducted by Lage et al. (2008) reported that mean hospital costs as dollars billed per patient in the year after the initial diagnosis of an SRE was $12,469, with the highest costs for radiation therapy ($5,930), pathologic fracture ($3,179), then bone surgery ($2,218). Another study of patients with advanced breast cancer conducted by Delea et al. (2006) reported billed average costs per SRE over 60 months (mean follow-up 13.8 months) among a limited subset of patients with SREs matched to patients without SREs and found that total medical care costs were $48,173 (95% confidence interval [CI] = $19,068-$77,684) greater in patients with SREs versus patients without SREs ($P=0.001). Since inpatient costs are a significant component of the total cost of care of SREs, focusing analysis on the inpatient setting enabled us to quantify the individual components that contribute to the per episode inpatient costs of SREs. Future studies will quantify the contribution of outpatient care and costs per SRE episode in these patient populations.

**Methods**

**Data Sources**

Data for this study were obtained from the MarketScan Commercial Claims & Encounter (commercial) database and the Medicare Supplemental & Coordination of Benefit (Medicare) database from Thomson Reuters. The databases are constructed based on claims and enrollment data provided by 138 medium to large employers and 13 health plans from across the United States. Data include medical claims for health care services performed in both the inpatient and outpatient settings and enrollment data, including member demographic information and eligibility and benefits data. The medical claims files include service dates, provider reimbursement amounts, patient copayment and deductible amounts, and Medicare coordination of benefit amounts where appropriate. The medical claims and enrollment data are linked to outpatient prescription drug claims through the use of unique enrollee identifiers. Together, the commercial and Medicare databases captured information on approximately 34.6 million covered lives in the working population and 2.5 million retirees in the Medicare population in 2008. The Medicare database profiles the health care experience of retirees and includes the Medicare-covered portion of payment, the employer-paid portion, and any patient out-of-pocket expenses. The database is compliant with the Health Insurance Portability and Accountability Act (HIPAA). Because this study did not involve the collection, use, or transmittal of individually identifiable data, Institutional Review Board (IRB) review or approval was not sought.
**Sample Selection**

The study sample consisted of patients with multiple myeloma, prostate cancer, or breast cancer with claims between January 1, 2003, and June 30, 2009. We selected SRE hospitalizations for patients who had (a) 2 or more claims at least 30 days apart with primary or secondary diagnosis of multiple myeloma (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] 203.xx), prostate cancer (ICD-9-CM 185.xx, V10.46), or breast cancer (ICD-9-CM 174.xx, 175.xx, V10.3) and (b) hospitalizations for one or more SREs as principal diagnosis (ICD-9-CM) or principal procedure (ICD-9-CM or Current Procedural Terminology [CPT]) at any time. In addition, at least 1 non-rule-out bone metastasis diagnosis (ICD-9-CM 198.5) before or on the date of admission was required for patients with prostate cancer or breast cancer.

SRE hospitalizations were further categorized using...
secondary diagnosis (ICD-9-CM) and/or secondary procedure (ICD-9-CM or CPT) codes indicative of local irreversible events defining an SRE. Diagnosis codes were used to identify pathologic fracture, surgery to bone, or spinal cord compression. Procedure codes were used to identify surgery to bone or spinal cord compression (Appendix). Although radiation to bone is also a local irreversible event, it was not included as an independent SRE in this study of inpatient costs because the procedure is primarily conducted in the outpatient setting. Hypercalcemia of malignancy, another recognized complication of bone metastases, is a systemic and potentially reversible event and was thus not considered to be a component of the SRE. Bone pain was similarly not included. Hospitalizations with negative or no reimbursed amounts were excluded from the analysis. In addition, hospitalizations within 30 days of a previous SRE hospitalization discharge date were excluded to avoid counting readmissions resulting from complications from the previous hospitalization.

### SRE Identification and Categorization

When secondary diagnosis or procedure codes for SREs were present in the claim, they were used to more precisely identify the type of SRE for which the patient was treated, as we assumed that, on average, 1 SRE per admission occurred and that the procedure was performed to treat the diagnosis

**TABLE 1**  
Demographic Characteristics and Hospitalization Discharge Status

<table>
<thead>
<tr>
<th></th>
<th>Prostate Cancer</th>
<th>Breast Cancer</th>
<th>Multiple Myeloma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of hospitalizations</strong></td>
<td>572</td>
<td>1,542</td>
<td>1,495</td>
</tr>
<tr>
<td><strong>Number of unique patients</strong></td>
<td>555 (100.0%)</td>
<td>1,413 (100.0%)</td>
<td>1,361 (100.0%)</td>
</tr>
<tr>
<td><strong>Mean [SD] age</strong></td>
<td>72.1 [11.6]</td>
<td>61.3 [12.8]</td>
<td>65.4 [12.5]</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>555 (100.0%)</td>
<td>31 (2.2)</td>
<td>667 (49.0)</td>
</tr>
<tr>
<td>Female</td>
<td>1,382 (97.8%)</td>
<td>649 (51.0)</td>
<td></td>
</tr>
<tr>
<td><strong>Age group (years)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Younger than 55</td>
<td>31 (5.6)</td>
<td>422 (29.9)</td>
<td>261 (19.2)</td>
</tr>
<tr>
<td>55-64</td>
<td>137 (24.7)</td>
<td>519 (36.7)</td>
<td>465 (34.2)</td>
</tr>
<tr>
<td>65-74</td>
<td>114 (20.5)</td>
<td>218 (15.4)</td>
<td>262 (19.3)</td>
</tr>
<tr>
<td>75 or older</td>
<td>273 (49.2)</td>
<td>254 (18.0)</td>
<td>373 (27.4)</td>
</tr>
<tr>
<td><strong>Geographic region</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Northeast</td>
<td>58 (10.5)</td>
<td>146 (10.3)</td>
<td>120 (8.8)</td>
</tr>
<tr>
<td>North central</td>
<td>166 (29.9)</td>
<td>421 (29.8)</td>
<td>485 (35.6)</td>
</tr>
<tr>
<td>South</td>
<td>195 (35.1)</td>
<td>569 (40.3)</td>
<td>504 (37.0)</td>
</tr>
<tr>
<td>West</td>
<td>132 (23.8)</td>
<td>268 (19.0)</td>
<td>248 (18.2)</td>
</tr>
<tr>
<td>Unknown</td>
<td>4 (0.7)</td>
<td>9 (0.6)</td>
<td>4 (0.3)</td>
</tr>
<tr>
<td><strong>Population density</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urban</td>
<td>477 (85.9)</td>
<td>1,200 (84.9)</td>
<td>1,137 (83.5)</td>
</tr>
<tr>
<td>Rural</td>
<td>78 (14.1)</td>
<td>213 (15.1)</td>
<td>224 (16.5)</td>
</tr>
<tr>
<td><strong>Payer</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Commercial</td>
<td>165 (29.7)</td>
<td>932 (66.0)</td>
<td>709 (52.1)</td>
</tr>
<tr>
<td>Medicare</td>
<td>390 (70.3)</td>
<td>481 (34.0)</td>
<td>652 (47.9)</td>
</tr>
<tr>
<td><strong>Discharge status</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Home</td>
<td>324 (58.4)</td>
<td>927 (65.6)</td>
<td>1,054 (77.4)</td>
</tr>
<tr>
<td>Death</td>
<td>15 (2.7)</td>
<td>36 (2.3)</td>
<td>19 (1.4)</td>
</tr>
<tr>
<td>Skilled nursing/rehabilitation facility</td>
<td>99 (17.8)</td>
<td>247 (17.5)</td>
<td>146 (10.7)</td>
</tr>
<tr>
<td>Acute care facility</td>
<td>47 (8.5)</td>
<td>88 (6.2)</td>
<td>81 (6.0)</td>
</tr>
<tr>
<td>Intermediate care or other facility</td>
<td>8 (1.4)</td>
<td>32 (2.3)</td>
<td>14 (1.0)</td>
</tr>
<tr>
<td>Other</td>
<td>79 (14.2)</td>
<td>212 (15.0)</td>
<td>181 (13.3)</td>
</tr>
</tbody>
</table>

*Study period was January 1, 2003, through June 30, 2009. Hospitalizations were identified with principal diagnosis (ICD-9-CM) and/or principal procedure (ICD-9-CM or CPT) codes indicative of local irreversible events defining an SRE. Diagnosis codes were used to identify pathologic fracture, surgery to bone, or spinal cord compression. Procedure codes were used to identify surgery to bone or spinal cord compression (Appendix). Patients had 2 or more claims at least 30 days apart with primary or secondary diagnosis of multiple myeloma (ICD-9-CM 203.0x), prostate cancer (ICD-9-CM 185.xx, V10.46), or breast cancer (ICD-9-CM 174.xx, 175.xx, V10.3). Patients with prostate or breast cancer also had at least 1 non-rule-out bone metastasis diagnosis (ICD-9-CM 198.5) on or before the date of admission.*

identified in the claim. For instance, surgery to bone includes procedures to set or stabilize a fracture or to prevent an imminent fracture or spinal cord compression. We verified our assumption in the breast cancer sample and found that, for all claims with spinal cord compression and surgery codes, the surgery location was to the spine. Similarly, for all claims with spinal cord compression and pathologic fracture codes, the location of the fracture was the vertebrae. For claims with pathologic fracture and surgery codes, the surgery site was consistent with the fracture site in all but 3% of cases.

Consequently, in cases where both surgery and pathologic fracture codes were present, we assumed that the surgery was to treat the pathologic fracture, and thus the SRE was classified as a pathologic fracture. In cases where both surgery and spinal cord compression codes were present, we assumed that surgery was to the spine and thus categorized the SRE as a spinal cord compression. In cases where both pathologic fracture and spinal cord compression codes were present, we assumed that the location of the fracture was the vertebrae and thus categorized the SRE as a spinal cord compression. This method created 3 mutually exclusive categories: spinal cord compression with or without pathologic fracture and/or surgery to the bone; pathologic fracture with or without surgery to the bone; and only surgery to the bone.

**Outcome Measures**

The primary study outcomes were payer costs and length of stay (LOS). Payer cost per SRE-associated hospitalization was measured as reimbursed amount paid by the health plan to a hospital, including the Medicare-paid portion, after subtracting patient copayments and deductibles. SRE-associated hospital costs included reimbursement of all claims for the full hospital stay until discharge for SRE-related hospitalizations as defined above. Start and end dates of service using room and board revenue codes were identified and all services within that duration, including professional services, were attributed to the hospital stay. Emergency room visits that resulted in the direct admission to the hospital were captured as inpatient admission costs. All costs were adjusted to June 2009 dollars using the medical care component of the Consumer Price Index.\(^1\)

LOS per SRE-associated hospitalization was calculated and was assessed by type of cancer and type of SRE.

**Statistical Analysis**

Payer costs and LOS for SRE-associated hospitalizations were examined using descriptive analyses that included descriptive profiles of patients’ demographic characteristics and hospital discharge status. In bivariate analyses, the distributions of payer cost and LOS per hospitalization were examined by type of cancer and type of SRE. In anticipation of a skewed cost distribution, we planned a priori to conduct a sensitivity analysis excluding extremely low or high costs of hospitalizations within the upper 1% and lower 1% of total costs to estimate their impact on mean payer costs and LOS.

To handle uncertainties in possible small sample sizes for less frequently occurring SREs (e.g., spinal cord compression), CIs for mean costs were estimated by the bootstrap method (repeated resampling with replacement from the original sample).\(^2\) The benefit of performing bootstrapping is that only one assumption is required, which is that the patients in this study were representative of the typical patient with advanced prostate or breast cancer or myeloma experiencing these events. We randomly selected a new sample of patients (with repeat patient selection possible) for each cohort of cancer and SRE type and estimated mean costs for each. We repeated this sampling 1,000 times to generate 1,000 estimates of mean cost for each cohort of SRE by tumor type. Confidence intervals (95%) were then constructed based on these 1,000 randomly drawn samples. All descriptive analyses were conducted using SAS version 9.1 (SAS Institute Inc., Cary, NC), and bootstrapping was conducted using Stata 11 (StataCorp, College Station, TX).

**Results**

**Demographic Characteristics and Discharge Status**

Patient demographic characteristics are reported in Table 1. The mean (SD) ages in years were 72.1 (11.6) for patients with...
Prostate cancer, 61.3 (12.8) for patients with breast cancer, and 65.4 (12.5) for patients with multiple myeloma. Approximately 70% of patients with prostate cancer, 33% of patients with breast cancer, and 47% of patients with multiple myeloma were 65 years or older. Across all cancer types, between 65% and 73% of patients lived in the southern or north central areas of the United States. This distribution reflects the regional distribution of covered lives in the MarketScan database and does not necessarily reflect the regional distribution of SRE-associated admissions in the United States. Across the cancer types, 58%-77% of patients were discharged to home, 11%-18% to rehabilitation facilities, and 6%-8% to acute care facilities. Between 1% and 3% of patients died during an SRE-associated hospitalization.

A total of 572 hospitalizations for prostate cancer, 1,542 for breast cancer, and 1,495 for multiple myeloma met the inclusion criteria (Figure 1). Between 4.5% and 6.4% (n=217) of hospitalizations were excluded from the study across the cancer types because they occurred within 30 days of a previous SRE hospitalization discharge date. For all 3 types of cancer, using
the mutually exclusive classification method, hospitalization occurred most often for pathologic fracture with or without surgery to the bone (Figure 2, Table 2). For prostate cancer, 21.3% of hospitalizations were categorized as surgery to the bone, 69.9% as pathologic fracture (with or without surgery to the bone), and 8.7% as spinal cord compression (with or without pathologic fracture and/or surgery to the bone). In the breast cancer cohort, 15.0% of hospitalizations were categorized as surgery to the bone, 79.0% as pathologic fracture, and 6.0% as spinal cord compression. In the multiple myeloma cohort, 23.6% of hospitalizations were categorized as surgery to the bone, 68.3% as pathologic fracture, and 8.1% as spinal cord compression.

Diagnosis and procedure codes for more than 1 SRE type were present in 244 (42.7%) of hospitalizations in the prostate cancer group, in 760 (49.3%) for breast cancer, and in 518 (34.6%) for multiple myeloma. The proportions of SRE code combinations that occurred under the spinal cord compression and pathologic fracture categories were generally similar across tumor types (Figure 2).

**Payer Costs and Length of Stay**

Table 3 reports mean health plan costs and LOS by type of cancer and type of SRE, again using the mutually exclusive categorization method. For patients with prostate cancer, mean (SD) payer costs were $42,094 ($70,746) for surgery to the bone, $22,390 ($28,042) for pathologic fracture, and $59,788 ($66,466) for spinal cord compression. Mean (SD) LOS per admission was 7.7 (9.1) days for surgery to the bone, 6.6 (5.6) days for pathologic fracture, and 11.6 (10.4) days for spinal cord compressions.

For patients with breast cancer, mean (SD) payer costs were $32,742 ($34,836) for surgery to the bone, $26,936 ($29,727) for pathologic fracture, and $59,854 ($59,334) for spinal cord compression. Mean (SD) LOS was 6.1 (5.3) days for surgery to the bone, 6.8 (6.2) days for pathologic fracture, and 9.4 (8.2) days for spinal cord compressions.

For patients with multiple myeloma, mean (SD) payer costs were $31,016 ($31,211) for surgery to the bone, $23,347 ($31,605) for pathologic fracture, and $43,691 ($53,986) for spinal cord compression. Mean (SD) LOS was 5.9 (7.4) days for surgery to the bone, 6.2 (7.4) days for pathologic fracture, and 7.6 (7.6) days for spinal cord compressions.

After excluding the upper 1% and lower 1% of reimbursement costs, mean cost estimates declined across all tumor types, ranging from $29,516 to $36,165 for surgery to the bone, $20,855 to $25,447 for pathologic fracture, and $39,957 to $58,012 for spinal cord compression. For prostate cancer, mean cost estimates decreased by 14.1% for patients experiencing surgery to the bone, 6.9% for pathologic fracture, and 6.5% for spinal cord compression. For breast cancer, mean cost estimates decreased by 6.1% for surgery to bone, 5.5% for

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Distribution of Health Plan Costs and Hospital Length of Stay for Selected Skeletal-Related Events</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prostate cancer</strong></td>
<td><strong>Pathologic Fracture</strong></td>
</tr>
<tr>
<td><strong>Health Plan Cost</strong></td>
<td><strong>Hospital LOS</strong></td>
</tr>
<tr>
<td>N</td>
<td>122</td>
</tr>
<tr>
<td>QL, Q3</td>
<td>$10,367, $43,318</td>
</tr>
<tr>
<td>Median</td>
<td>$20,641</td>
</tr>
<tr>
<td>Min-Max</td>
<td>$1,333-$649,392</td>
</tr>
<tr>
<td><strong>Breast cancer</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Health Plan Cost</strong></td>
<td><strong>Hospital LOS</strong></td>
</tr>
<tr>
<td>N</td>
<td>231</td>
</tr>
<tr>
<td>QL, Q3</td>
<td>$11,645, $43,734</td>
</tr>
<tr>
<td>Median</td>
<td>$20,269</td>
</tr>
<tr>
<td>Min-Max</td>
<td>$1,483-$311,701</td>
</tr>
<tr>
<td><strong>Multiple myeloma</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Health Plan Cost</strong></td>
<td><strong>Hospital LOS</strong></td>
</tr>
<tr>
<td>N</td>
<td>353</td>
</tr>
<tr>
<td>QL, Q3</td>
<td>$11,991, $38,834</td>
</tr>
<tr>
<td>Median</td>
<td>$22,642</td>
</tr>
<tr>
<td>Min-Max</td>
<td>$0-$218,337</td>
</tr>
</tbody>
</table>

*Categories of patients were mutually exclusive. Hospitalizations for pathologic fractures are with or without surgery to the bone, and hospitalizations for spinal cord compression are with or without surgery to the bone.

+Reimbursed amount paid by the health plan, including the Medicare-paid portion, after subtracting patient copayments and deductibles.

+With metastasis to the bone.

LOS = length of stay; Q1 = quartile 1 (25th percentile); Q3 = quartile 3 (75th percentile); SD = standard deviation.
The use of a composite approach to identify SREs allowed us to develop a composite view of each SRE, thus better reflecting what is occurring in patients. For example, the composition of spinal cord compression as an SRE allowed up to 4 possible combinations of coding: spinal cord compression only, spinal cord compression plus pathologic fracture, spinal cord compression plus surgery to the bone, or spinal cord compression plus pathologic fracture and surgery to bone. Since each of these 4 possibilities is represented in the spinal cord compression claims selected in our study across tumor types, we are more confident that the average costs calculated here provide a reliable estimate of the inpatient costs.

Lastly, we conducted sensitivity analyses to account for skewed cost distributions and potentially small samples of patients in the subgroups of SRE and cancer type. After removing the outliers, the mean cost estimates did not change substantially for the majority of SREs across tumor types.

### Limitations

First, the study was limited to SREs in inpatient settings only. Results do not represent the cost of SREs overall or of treatments provided in outpatient settings. Moreover, the study patients represent only a portion of patients with SREs because not all patients with SREs are treated in inpatient settings. Second, the results represent net payer cost after subtracting patient copayments and deductibles, rather than total allowed cost. To address the possibility that exclusion of patient paid amounts affected our findings, we analyzed the percentage of costs paid by patients and found that it was small, ranging from 1.5% to 4.2% of total cost depending on tumor type and SRE type. Third, a common limitation in studies using administrative health care databases is selecting claims based on ICD-9-CM and CPT codes that accurately represent the specific population of interest and clinical endpoints such as SRE-associated hospitalizations. To minimize the potential bias in selecting claims and improve the specificity for selecting the correct population in our study, we consulted with an independent coding expert to identify a list of codes for extracting SRE-associated hospitalizations for this analysis. Fourth, our analysis is based on a sample of patients covered by health care plans from medium to large employers and some who are also covered by Medicare (dual-eligibility). The results from our study may not reflect the full spectrum of reimbursed amounts for these SRE-associated hospitalizations and might have limited generalizability. Fifth, we assumed that patients identified in this database are typical patients with cancer and bone metastasis. Patient age in these populations is consistent with the SEER database; however, no further comparisons were made.

### Discussion

Bone lesions secondary to advanced malignancies are a common occurrence and can have devastating clinical consequences in patients. Patients with bone lesions can experience burdensome SREs such as pathologic fracture, spinal cord compression, or need for surgery or radiation to bone. These skeletal complications are also important from a health economic perspective in prostate and breast cancers, given the prevalence of these diseases, and in multiple myeloma due to the extent of bone destruction that occurs with the disease.

In this study, we used 2 large national claims databases to estimate the mean costs that third-party payers incur for reimbursing SRE-associated hospitalizations (excluding radiation to bone, hypercalcemia of malignancy, and bone pain) among patients with multiple myeloma or bone metastasis secondary to prostate or breast cancer. Mean hospital reimbursements were higher across tumor types for spinal cord compression with or without pathologic fracture and/or surgery to the bone ($43,691-$59,854) than for surgery to the bone only ($31,016-$42,094) or pathologic fracture with or without surgery to the bone ($22,390-$26,936).

The mutually exclusive categorizations used to classify claims under 1 SRE when more than 1 SRE code was present allowed us to develop a composite view of each SRE, thus better reflecting what is occurring in patients. For example, the composition of spinal cord compression as an SRE allowed up to 4 possible combinations of coding: spinal cord compression only, spinal cord compression plus pathologic fracture, spinal cord compression plus surgery to the bone, or spinal cord compression plus pathologic fracture and surgery to bone. Since each of these 4 possibilities is represented in the spinal cord compression claims selected in our study across tumor types, we are more confident that the average costs calculated here provide a reliable estimate of the inpatient costs.

Lastly, we conducted sensitivity analyses to account for skewed cost distributions and potentially small samples of patients in the subgroups of SRE and cancer type. After removing the outliers, the mean cost estimates did not change substantially for the majority of SREs across tumor types.

### Limitations

First, the study was limited to SREs in inpatient settings only. Results do not represent the cost of SREs overall or of treatments provided in outpatient settings. Moreover, the study patients represent only a portion of patients with SREs because not all patients with SREs are treated in inpatient settings. Second, the results represent net payer cost after subtracting patient copayments and deductibles, rather than total allowed cost. To address the possibility that exclusion of patient paid amounts affected our findings, we analyzed the percentage of costs paid by patients and found that it was small, ranging from 1.5% to 4.2% of total cost depending on tumor type and SRE type. Third, a common limitation in studies using administrative health care databases is selecting claims based on ICD-9-CM and CPT codes that accurately represent the specific population of interest and clinical endpoints such as SRE-associated hospitalizations. To minimize the potential bias in selecting claims and improve the specificity for selecting the correct population in our study, we consulted with an independent coding expert to identify a list of codes for extracting SRE-associated hospitalizations for this analysis. Fourth, our analysis is based on a sample of patients covered by health care plans from medium to large employers and some who are also covered by Medicare (dual-eligibility). The results from our study may not reflect the full spectrum of reimbursed amounts for these SRE-associated hospitalizations and might have limited generalizability. Fifth, we assumed that patients identified in this database are typical patients with cancer and bone metastasis. Patient age in these populations is consistent with the SEER database; however, no further comparisons were made.

<table>
<thead>
<tr>
<th>TABLE 4</th>
<th>Mean Health Plan Costs\textsuperscript{a} and 95% Bootstrapped Confidence Intervals for Hospitalizations for Selected SREs by SRE Type and Tumor Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery to the bone</td>
<td></td>
</tr>
<tr>
<td>Prostate cancer\textsuperscript{b}</td>
<td>$42,094 ($29,247-$54,941)</td>
</tr>
<tr>
<td>Breast cancer\textsuperscript{b}</td>
<td>$32,742 ($28,417-$37,067)</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>$31,016 ($27,823-$34,210)</td>
</tr>
<tr>
<td>Pathologic fracture\textsuperscript{c}</td>
<td></td>
</tr>
<tr>
<td>Prostate cancer\textsuperscript{b}</td>
<td>$22,390 ($19,506-$25,273)</td>
</tr>
<tr>
<td>Breast cancer\textsuperscript{b}</td>
<td>$26,936 ($22,248-$28,625)</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>$23,347 ($21,435-$25,260)</td>
</tr>
<tr>
<td>Spinal cord compression\textsuperscript{c}</td>
<td></td>
</tr>
<tr>
<td>Prostate cancer\textsuperscript{b}</td>
<td>$59,788 ($41,401-$78,176)</td>
</tr>
<tr>
<td>Breast cancer\textsuperscript{b}</td>
<td>$59,854 ($47,771-$71,937)</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>$43,691 ($34,198-$53,180)</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Reimbursed amount paid by the health plan, including the Medicare-paid portion, after subtracting patient copayments and deductibles.

\textsuperscript{b}With metastasis to the bone.

\textsuperscript{c}Categorizations are mutually exclusive. Hospitalizations for pathologic fracture are with or without surgery to the bone, and hospitalizations for spinal cord compression are with or without pathologic fracture and/or surgery to the bone.

CI = confidence interval; SRE = skeletal-related event.

No further comparisons were made.
Payer Costs for Inpatient Treatment of Pathologic Fracture, Surgery to Bone, and Spinal Cord Compression Among Patients with Multiple Myeloma or Bone Metastasis Secondary to Prostate or Breast Cancer

Conclusions
The inpatient costs associated with treating SREs are significant from a payer perspective. The present study used a careful process for patient selection and a mutually exclusive categorization method that assessed heterogeneity among SRE types and tumor types. This study provides an estimate that is helpful to payers in quantifying the inpatient financial impact of cancer-related SREs. SREs place a substantial burden on patients with advanced tumors and on third-party payers.

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DISCLOSURES
This work was supported by Amgen Inc., which is developing denosumab, one of the products discussed in this article. Denosumab is presently approved by the U.S. Food and Drug Administration only for the treatment of postmenopausal women with osteoporosis at high risk for fracture, at a dose of 60 mg administered by subcutaneous injection every 6 months. Three authors are employees of and own stock in Amgen Inc. The remaining 2 authors are employed by Thomson Reuters, which received funds from Amgen to conduct the analyses presented in this article.

Concept and design were the work of Barlev, with the assistance of Chung and Song. Ivanov, Song, and Barlev collected the data. Barlev interpreted the data, assisted by Chung, Song, and Setty. All authors shared in writing the manuscript. Setty and Barlev had primary responsibility for revisions.

ACKNOWLEDGEMENT
The authors would like to thank George A. Goldberg, MD, of i3 Innovus for identification of ICD-9-CM and CPT codes.

REFERENCES
## APPENDIX

### Codes to Identify Selected Inpatient SREs

<table>
<thead>
<tr>
<th>Condition</th>
<th>ICD-9-CM Codes</th>
<th>CPT Codes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathologic fracture</td>
<td>733.1x</td>
<td>22325-22328, 22520-22522, 22532-22632, 23515, 23615-23616, 23630, 24515-24516, 24538, 24545-24546, 24566-24575, 24579, 24582, 24586, 24587, 24635, 24665, 24666-24685, 25315, 25525-25526, 25545, 25600-25609, 27215-27218, 27226-27228, 27235, 27236, 27244, 27245, 27248, 27269, 27506, 27507, 27509, 27511-27514, 27524, 27535-27536, 27540, 27735, 27758, 27759, 27766, 27769, 27784, 27792, 27826, 27827</td>
</tr>
<tr>
<td>Spinal cord compression</td>
<td>721 1, 721 4, 721 41, 721 42, 721 91, 722 7, 722 70, 722 71-722 73, 336 9</td>
<td>63050, 63051</td>
</tr>
</tbody>
</table>

All-Cause Health Care Utilization and Costs Associated with Newly Diagnosed Multiple Sclerosis in the United States

Carl V. Asche, PhD, MBA; Mendel E. Singer, PhD; Mehul Jhaveri, PharmD, MPH; Hsingwen Chung, BS Pharm, MS; and Aaron Miller, MD

ABSTRACT

BACKGROUND: Multiple sclerosis (MS) is a costly and crippling neurologic disease. Approximately 250,000 to 400,000 persons in the United States are currently diagnosed with MS. Most individuals experience their first symptoms between the ages of 20 and 40 years; therefore, this disease may have substantial impact over many years of life on health, quality of life, productivity, and employment. Whereas a number of studies have utilized a cross-sectional design to evaluate the costs associated with MS, no study has used a large administrative claims database to analyze the direct costs associated with newly diagnosed MS.

OBJECTIVE: To estimate the additional health care utilization and costs in otherwise healthy patients with newly diagnosed MS.

METHODS: This was a retrospective cohort analysis of the Medstat MarketScan Commercial Claims and Encounters database, which is composed of medical and pharmacy claims for approximately 8 million beneficiaries from 45 U.S. commercial health plans. Cases extracted from the database included adults aged 18 to 64 years with either (a) at least 2 medical claims with a diagnosis of MS (ICD-9-CM code 340) in any diagnosis field on the claim or (b) 1 prescription (medical or pharmacy) claim for injectable MS drug therapy (interferon beta-1a, interferon beta-1b, glatiramer acetate) for dates of service between January 1, 2004, and December 31, 2006. Natalizumab was not used to identify MS cases, but was used to exclude potential comparison group subjects. The index date for patients with MS was the first qualifying diagnosis or pharmacy claim. Each MS patient was matched to 5 “healthy comparison” cases without MS diagnoses or treatment using the following variables: region, insurance type, gender, relation to employee, age, and enrollment period. Cases with any condition listed in the Charlson Comorbidity Index were excluded from both the MS and “healthy comparison” cohorts. Each “healthy comparison” case was assigned the index date of the matching MS patient. Continuous enrollment 12 months pre- and post-index was required for both the MS and “healthy comparison” groups. Costs broken down by type of utilization were adjusted to 2010 dollars using the appropriate medical component of the Consumer Price Index. Use of services and costs were compared using chi-square, t-tests, parametric and nonparametric tests.

RESULTS: 1,411 MS cases (65.6% female) were matched to 7,055 “healthy comparison” cases (65.6% female). In the analyses of all-cause health care services during the 12-month post-index period, MS patients were significantly more likely to use all categories of health services examined. Compared with the “healthy comparison” group, new MS patients were 3.5 times as likely to be hospitalized (15.2% vs. 4.3% for MS vs. comparison, respectively), twice as likely to have at least 1 emergency room (ER) visit (25.5% vs. 12.2%) and 2.4 times as likely to have at least 1 visit for physical, occupational, or speech therapy (23.7% vs. 9.9%; P<0.001 for all comparisons). MS patients also had higher mean 12-month costs related to each category of service (inpatient services $4,110 vs. $896; radiology services $1,693 vs. $259; ER $432 vs. $189; office visits $849 vs. $310; therapies $295 vs. $81, respectively; all P-values <0.001). Total mean 12-month all-cause health care costs were significantly higher for MS patients than for the “healthy comparison” group ($18,829 vs. $4,038, respectively, P<0.001). Claims attributed to MS by diagnosis code in any field on the claim or use of an MS injectable drug accounted for a mean cost of $8,839 (46.9%), and MS injectable drugs accounted for $4,573 (24.3%) of total all-cause health care costs.

CONCLUSIONS: Newly diagnosed MS patients have significantly higher rates of hospitalizations, radiology services, and ER and outpatient visits compared with non-MS “healthy comparison” patients. MS presents a considerable burden to the U.S. health care system within the first year of diagnosis.

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What is already known about this subject

• The economic burden associated with multiple sclerosis (MS) is substantial. Patients with MS incur medical costs 2 to 3 times those of all enrollees in a managed care organization.
• The majority of total costs incurred by patients with MS are direct medical costs. In a cross-sectional study of U.S. patients with MS, 94% of whom were using disease-modifying drugs (DMDs), Kobelt et al. (2006) found that 34% of total costs (direct and indirect) were attributable to DMDs.

What this study adds

• This is the first such study to assess the direct health care costs and resource utilization among newly diagnosed MS patients compared with healthy members of commercial health plans. Overall medical costs were 4.7 times higher for newly diagnosed MS patients.
• Less than one-half of the nearly $19,000 in the first 12 months of costs after diagnosis of MS could be attributed to medical claims with diagnosis codes for MS in any field on the claim.
• MS injectable drugs accounted for approximately one-fourth of total direct medical costs for newly diagnosed MS patients in the first 12 months after diagnosis.
multiple sclerosis (MS) is a costly and crippling neurologic disease. Approximately 250,000 to 400,000 persons in the United States are currently diagnosed with MS.1,2 Most individuals experience their first symptoms between the ages of 20 and 40 years; therefore, this disease may have substantial impact over many years of life on their health, quality of life, productivity and employment.3 As a consequence, the economic costs associated with MS are significant.4

Managing MS requires both pharmacologic and nonpharmacologic treatments to prevent disease progression and control a variety of related disorders. Specific disorders related to the progression of MS may require physical therapy, occupational therapy, medical devices, counseling, or medications. These disorders include fatigue, bladder or bowel dysfunction, urinary tract infections, muscular weakness, spasticity, joint contractures, difficulty walking, tremor, vision disturbances, pain, loss of cognition, depression and anxiety, speech and swallowing difficulty, sexual dysfunction, and pressure ulcers.5 The objectives of the treatment of MS are to avoid temporary disability attributed to relapses and to delay progression to permanent disability.

Two published studies and 1 poster abstract have used cross-sectional designs to evaluate the costs associated with MS and MS relapses.6–8 and 2 studies have evaluated direct and indirect costs of the disease through surveys.9,10 No published studies in the literature used data from a large, nationally representative administrative claims database to evaluate the direct costs (e.g., medical, pharmacy) of newly diagnosed MS patients. One needs to be able to estimate the trade-offs involved in introducing costly treatment to newly diagnosed MS patients.

The purpose of this study was to examine the burden on the U.S. health care system, in service use and cost, associated with newly diagnosed MS by assessing the direct costs and resource utilization (inpatient, outpatient, pharmacy, and emergency room [ER] visits) associated with MS diagnosis or treatment compared with a matched “healthy comparison” group from a U.S. managed care perspective in an adult population aged 65 years or younger.

**Methods**

This was a retrospective analysis utilizing a large, nationally representative administrative U.S. claims database, the Medstat MarketScan Commercial Claims and Encounters (CCE) dataset. The CCE dataset contains the health care experience of approximately 8 million employees and their dependents (annually) covered under preferred provider organizations, point-of-service plans, indemnity plans, and health maintenance organizations. In addition, the database provides data on hospitalizations, ER visits, diagnosis, age of patient, gender, geographic location, inpatient and outpatient services, and outpatient prescription drugs. Medstat has separate files for inpatient, outpatient (includes ER, hospital outpatient, and physician visits) and outpatient pharmacy claims. The definitions depicted in Table 1 reflect the manner in which the service categories were assigned whereby the appropriate procedure codes were assigned according to the injections, MS drugs, physician visits, neurologist visits (subset of physician visits), laboratory, physical therapy, occupational therapy, and swallowing therapy. The Medstat database links enrollment and medical claims for inpatient, outpatient, and outpatient prescription drug services for each patient using encrypted identifiers. The data are drawn from roughly 45 large employers, health plans, and government organizations.

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**TABLE 1 Service Types and Drug Codes**

<table>
<thead>
<tr>
<th>Services</th>
<th>Codes Used</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Service types</strong></td>
<td></td>
</tr>
<tr>
<td>Occupational therapy</td>
<td>Service code 114</td>
</tr>
<tr>
<td>Physical therapy</td>
<td>Service code 115</td>
</tr>
<tr>
<td>Speech and language therapy</td>
<td>Service code 116</td>
</tr>
<tr>
<td><strong>Injections</strong></td>
<td></td>
</tr>
<tr>
<td>MS drugs - any of the following procedure codes: J1830, J1825, Q3025, Q3026, J1195, Q2010, Q4079</td>
<td></td>
</tr>
<tr>
<td>Physician office visits</td>
<td>Any of the following CPT codes: 99201-99205, 99211-99215, 99241-99245, 99271-99274, 99381-99387, 99391-99397, 99401-99404, 99420, 99429</td>
</tr>
<tr>
<td>Neurologist office visits</td>
<td>Field listed as 260, which is neurologist</td>
</tr>
<tr>
<td>Laboratory</td>
<td>CPT code 89999 (i.e., 80000-89999)</td>
</tr>
<tr>
<td>Radiology</td>
<td>CPT 79999 (i.e., 70000-79999)</td>
</tr>
<tr>
<td>PT/OT/speech, swallowing therapy</td>
<td>Service field = 114-116, which is therapy</td>
</tr>
<tr>
<td><strong>Drugs</strong></td>
<td></td>
</tr>
<tr>
<td>Glatiramer acetate</td>
<td>NDC Numbers (First 9 Characters)</td>
</tr>
<tr>
<td></td>
<td>00088115003; 00088115330; 68115070503; 68546031730c</td>
</tr>
<tr>
<td>Interferon beta-1a</td>
<td>44087002203; 44087004403; 44087882201; 54569443300c; 59627000103; 59627000205</td>
</tr>
<tr>
<td>Interferon beta-1b</td>
<td>50419052103; 50419052115; 50419052315; 50419052325; 50419052335c</td>
</tr>
<tr>
<td>Natalizumab</td>
<td>59075073015b</td>
</tr>
<tr>
<td>J Codes</td>
<td></td>
</tr>
<tr>
<td>Glatiramer acetate</td>
<td>J1195, Q2010</td>
</tr>
<tr>
<td>Interferon beta-1a</td>
<td>J1825, Q3025</td>
</tr>
<tr>
<td>Interferon beta-1b</td>
<td>J1830, Q3026</td>
</tr>
<tr>
<td>Natalizumab</td>
<td>Q4079</td>
</tr>
</tbody>
</table>

---

499% of the therapies were captured using the occupational, physical and speech and language therapies. Also used specific CPT/HCPCS codes which accounted for the remaining 01% of the therapies: 97001-97799, 92506-92508, 92526; HCPCS codes G0152, G0153, S9128, 95256.

*Measured only during the 12-month follow-up, not during sample selection.

*No claims were found with this NDC number.

*All of these J codes appeared in the database.

*CPT = Current Procedural Terminology; HCPCS = Healthcare Common Procedure Coding System; MS = multiple sclerosis; NDC = national drug code; OT = occupational therapy; PT = physical therapy.
Cases extracted from the CCE dataset included adults (aged 18 to 64 years) with (a) a diagnosis code for MS (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] = 340) in any claim field (i.e., primary, secondary, or other) on at least 2 claims (inpatient or outpatient medical), or (b) at least 1 outpatient pharmacy claim for MS treatment including interferon-beta 1a (Avonex [Biogen Idec] or Rebif [Pfizer]), interferon-beta 1b (Betaseron [Bayer]), or glatiramer acetate (Copaxone [Teva Pharmaceuticals]) for MS treatment with dates of service between January 1, 2004, and December 31, 2006. Natalizumab (Tysabri [Elan]) was counted as an MS-related drug in the analysis of utilization and cost, and for excluding potential comparison group subjects. However, it was not used for the purpose of identifying MS cases.

The first qualifying MS diagnosis (ICD-9-CM 340, any listed diagnosis) or MS-specific treatment medication was considered to be the index event. Whenever inpatient records were checked for an MS diagnosis, only the admission claim record (up to 15 listed diagnosis codes) was used, and not line-item charges. Thus, an inpatient record with a line item with an
MS diagnosis code was not considered an MS claim if the MS diagnosis code failed to make it into the header claim's list of up to 15 diagnoses.

Patients were excluded if they were not continuously enrolled for at least 12 months pre-index event and at least 12 months post-index event or if they were missing necessary data elements (e.g., age, gender, location, plan type, or diagnosis codes). Patients were also excluded if they had an MS diagnosis or treatment within 12 months prior to the index date.

Each qualifying MS case was matched to 5 “healthy comparison” group enrollees with the same geographic region of country, insurance type, gender, relation to employee, and age of patient at index event date (year of birth within 3 years). “Healthy comparison” group enrollees could not have an MS diagnosis code or MS treatment drug in the study period. “Healthy comparison” group enrollees also had matching enrollment—that is, they were enrolled at the time of the index date of the matched MS patient, and were continuously enrolled from 12 months prior to the index date to at least 12 months following the index date. The inclusion of 5 matched “healthy comparison” group enrollees rather than 1:1 matching was to improve power. Both MS patients and “healthy comparison” group enrollees were excluded if they had a history of any condition in the Charlson Comorbidity Index (CCI) during the 12 months prior to the index date. All listed diagnosis codes were used for this purpose. Excluding people with comorbid conditions allowed for analyses that isolate the impact of newly diagnosed MS. It also avoids the difficulty in controlling for severity of comorbidities.

### Statistical Analysis Plan

Utilization rates and costs for prescription drugs and health

---

**TABLE 2** Demographic Characteristics

<table>
<thead>
<tr>
<th>Demographic Characteristics (All Used for Matching)</th>
<th>MS Patient Cohort</th>
<th>Healthy Comparison Cohort</th>
<th>Full Sample</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 1,411</td>
<td>n = 7,055</td>
<td>n = 8,466</td>
</tr>
<tr>
<td>Mean [SD] age</td>
<td>43.2 [12.8]</td>
<td>44.2 [12.8]</td>
<td>44.1 [12.8]</td>
</tr>
<tr>
<td></td>
<td>% (n)</td>
<td>% (n)</td>
<td>% (n)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>65.6 (926)</td>
<td>65.6 (4,630)</td>
<td>65.6 (5,556)</td>
</tr>
<tr>
<td>Male</td>
<td>34.3 (485)</td>
<td>34.4 (2,425)</td>
<td>34.3 (2,910)</td>
</tr>
<tr>
<td>Relationship to primary insured</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Self</td>
<td>68.0 (960)</td>
<td>68.0 (4,800)</td>
<td>68.0 (5,760)</td>
</tr>
<tr>
<td>Spouse</td>
<td>23.1 (326)</td>
<td>23.1 (1,630)</td>
<td>23.1 (1,956)</td>
</tr>
<tr>
<td>Child or other dependent</td>
<td>8.9 (125)</td>
<td>8.9 (625)</td>
<td>8.9 (750)</td>
</tr>
<tr>
<td>U.S. Bureau of Census region</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>North central</td>
<td>31.3 (441)</td>
<td>31.3 (2,205)</td>
<td>31.3 (2,646)</td>
</tr>
<tr>
<td>Northeast</td>
<td>12.0 (170)</td>
<td>12.1 (850)</td>
<td>12.1 (1,020)</td>
</tr>
<tr>
<td>South</td>
<td>33.4 (471)</td>
<td>33.4 (2,355)</td>
<td>33.4 (2,826)</td>
</tr>
<tr>
<td>West</td>
<td>23.3 (329)</td>
<td>23.3 (1,645)</td>
<td>23.3 (1,974)</td>
</tr>
<tr>
<td>Insurance plan type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Noncapitated point of service</td>
<td>24.7 (349)</td>
<td>24.7 (1,745)</td>
<td>24.7 (2,093)</td>
</tr>
<tr>
<td>Preferred provider organization</td>
<td>27.5 (388)</td>
<td>27.5 (1,940)</td>
<td>27.5 (2,328)</td>
</tr>
<tr>
<td>Capitated point of service</td>
<td>3.3 (46)</td>
<td>3.3 (230)</td>
<td>3.3 (276)</td>
</tr>
<tr>
<td>Health maintenance organization</td>
<td>33.5 (472)</td>
<td>33.5 (2,360)</td>
<td>33.5 (2,832)</td>
</tr>
<tr>
<td>Comprehensive&lt;sup&gt;b&lt;/sup&gt;</td>
<td>11.1 (156)</td>
<td>11.1 (780)</td>
<td>11.1 (936)</td>
</tr>
<tr>
<td>Identification year</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2004</td>
<td>43.2 (609)</td>
<td>43.2 (3,045)</td>
<td>43.2 (3,654)</td>
</tr>
<tr>
<td>2005</td>
<td>30.3 (427)</td>
<td>30.3 (2,135)</td>
<td>30.3 (2,562)</td>
</tr>
<tr>
<td>2006</td>
<td>26.6 (375)</td>
<td>26.6 (1,875)</td>
<td>26.6 (2,250)</td>
</tr>
<tr>
<td>Method of identification</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MS diagnosis only</td>
<td>96.0 (1,354)</td>
<td>Not applicable</td>
<td>Not applicable</td>
</tr>
<tr>
<td>MS medication only</td>
<td>3.8 (54)</td>
<td>Not applicable</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Both MS diagnosis and MS medication&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.2 (3)</td>
<td>Not applicable</td>
<td>Not applicable</td>
</tr>
</tbody>
</table>

<sup>a</sup>Both cohorts excluded patients with any comorbidities, identified using the Charlson Comorbidity Index, measured using any diagnosis code on the claim during the 12 months prior to the index date.

<sup>b</sup>Comprehensive insurance plan denotes major medical which is synonymous with indemnity plan.

<sup>c</sup>Indicates that patient had both a diagnosis and a claim for MS medication on the same day.

MS = multiple sclerosis; SD = standard deviation.
care services were compared for the MS patient cohort and “healthy comparison” group. Drug use was categorized for many drug categories commonly used in patients with MS: adrenals, amphetamines, anticonvulsants, antidepressants, antipsychotics, urinary antibiotics. These categories were based on therapeutic drug class according to the Red Book, which is included in the Medstat database (Appendix).\(^{12}\) Prescription drug use and health care service utilization were evaluated in terms of whether certain types of drugs or services were used, and how frequently. Drug cost was assessed as the ingredient cost, which represents the discount below the average wholesale price, plus the dispensing fee. Service utilization cost was the gross average payment to the provider, and represents the amount eligible for payment under the medical plan. Mean costs were determined overall and by categories of drug use and service utilization. Costs were adjusted to 2010 utilizing the Consumer Price Index. Services with an MS diagnosis in any diagnosis field on the claim were also described.

For statistical analysis, comparison of categorical variables was done using chi-square tests with Fisher’s exact test used for comparison of 2 dichotomous variables. Comparison of continuous variables was handled conservatively, using the

<table>
<thead>
<tr>
<th>TABLE 3</th>
<th>Prescription Drug Utilization in 12-Month Post-Index Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prescription Medication Utilization</td>
<td>MS Patient Cohort(^a)</td>
</tr>
<tr>
<td></td>
<td>n = 1,411</td>
</tr>
<tr>
<td><strong>MS drugs</strong>(^c)</td>
<td></td>
</tr>
<tr>
<td>Patients with any pharmacy claim % (n)</td>
<td>30.8% (435)</td>
</tr>
<tr>
<td>Mean [SD] number of pharmacy claims</td>
<td>2.30 [4.06]</td>
</tr>
<tr>
<td>Mean [SD] number of pharmacy claims per user</td>
<td>7.46 [3.89]</td>
</tr>
<tr>
<td><strong>Anticonvulsants</strong></td>
<td></td>
</tr>
<tr>
<td>Patients with any pharmacy claims % (n)</td>
<td>21.2% (299)</td>
</tr>
<tr>
<td>Mean [SD] pharmacy claims</td>
<td>1.20 [3.56]</td>
</tr>
<tr>
<td>Mean [SD] pharmacy claims per user</td>
<td>5.67 [3.87]</td>
</tr>
<tr>
<td><strong>Antidepressants</strong></td>
<td></td>
</tr>
<tr>
<td>Patients with any pharmacy claims % (n)</td>
<td>33.1% (467)</td>
</tr>
<tr>
<td>Mean [SD] pharmacy claims</td>
<td>2.08 [4.00]</td>
</tr>
<tr>
<td>Mean [SD] pharmacy claims per user</td>
<td>6.28 [4.67]</td>
</tr>
<tr>
<td><strong>Antipsychotics</strong></td>
<td></td>
</tr>
<tr>
<td>Patients with any pharmacy claims % (n)</td>
<td>2.4% (34)</td>
</tr>
<tr>
<td>Mean [SD] pharmacy claims</td>
<td>0.09 [0.73]</td>
</tr>
<tr>
<td>Mean [SD] pharmacy claims per user</td>
<td>3.71 [3.00]</td>
</tr>
<tr>
<td><strong>Urinary antibiotics</strong></td>
<td></td>
</tr>
<tr>
<td>Patients with any pharmacy claims % (n)</td>
<td>3.8% (54)</td>
</tr>
<tr>
<td>Mean [SD] pharmacy claims</td>
<td>0.07 [0.50]</td>
</tr>
<tr>
<td>Mean [SD] pharmacy claims per user</td>
<td>1.94 [3.63]</td>
</tr>
<tr>
<td><strong>Amphetamines</strong></td>
<td></td>
</tr>
<tr>
<td>Patients with any pharmacy claims % (n)</td>
<td>7.3% (103)</td>
</tr>
<tr>
<td>Mean [SD] pharmacy claims</td>
<td>0.29 [1.43]</td>
</tr>
<tr>
<td>Mean [SD] pharmacy claims per user</td>
<td>4.00 [3.63]</td>
</tr>
<tr>
<td><strong>Adrenals</strong></td>
<td></td>
</tr>
<tr>
<td>Patients with any pharmacy claims % (n)</td>
<td>25.4% (358)</td>
</tr>
<tr>
<td>Mean [SD] pharmacy claims</td>
<td>0.55 [1.46]</td>
</tr>
<tr>
<td>Mean [SD] pharmacy claims per user</td>
<td>2.15 [2.23]</td>
</tr>
<tr>
<td><strong>All other prescription drugs</strong></td>
<td></td>
</tr>
<tr>
<td>Patients with any pharmacy claims % (n)</td>
<td>86.8% (1,225)</td>
</tr>
<tr>
<td>Mean [SD] pharmacy claims</td>
<td>15.20 [18.29]</td>
</tr>
<tr>
<td>Mean [SD] pharmacy claims per user</td>
<td>17.53 [18.57]</td>
</tr>
</tbody>
</table>

\(^a\)Both cohorts excluded patients with any comorbidities, identified using the Charlson Comorbidity Index, measured using any diagnosis code on the claim during the 12 months prior to the index date.

\(^b\)P value for Fisher’s exact test for proportions and Wilcoxon rank-sum (also known as Mann-Whitney U) test for continuous variables, comparing the MS patient and healthy comparison cohorts.

\(^c\)Does not include injectable MS medications reported on medical claims. 1.4% of patients in the MS cohort had no pharmacy claims for MS injectable drugs but had at least 1 medical claim for an MS injectable drug.

MS = multiple sclerosis; SD = standard deviation.
In this sample, 30.8% of MS patients filled prescriptions for MS treatment drugs, and another 1.4% did not have a pharmacy claim for an MS treatment drug but did have it administered in a physician’s office or ER (Table 3). Thus, a total of 32.2% received an injectable MS treatment drug during the year of follow-up. These patients had an average of 7.5 pharmacy claims. In all drug categories examined, the MS patient cohort had significantly ($P < 0.001$) higher use than the “healthy comparison” cohort. This was particularly noteworthy when comparing use of anticonvulsants (21.2% with MS group vs. 3.4% among “healthy comparison” enrollees, $P < 0.001$), antidepressants (33.1% with MS group vs. 14.6% among “healthy comparison” enrollees, $P < 0.001$), antipsychotics (2.4% with MS group vs. 0.6% among “healthy comparison” enrollees, $P < 0.001$), and amphetamines (7.3% with MS group vs. 1.2% among “healthy comparison” enrollees, $P < 0.001$). Among users of anticonvulsants, MS patients had a mean of

<table>
<thead>
<tr>
<th>TABLE 4 Health Care Services Utilization in 12-Month Post-Index Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Health Care Service Utilization</td>
</tr>
<tr>
<td>---------------------------------</td>
</tr>
<tr>
<td><strong>Inpatient admissions</strong></td>
</tr>
<tr>
<td>Patients with any admission % (n)</td>
</tr>
<tr>
<td>Mean [SD] number of admissions</td>
</tr>
<tr>
<td>Mean [SD] number of admissions per user</td>
</tr>
<tr>
<td><strong>ER visits</strong></td>
</tr>
<tr>
<td>Patients with any ER visits % (n)</td>
</tr>
<tr>
<td>Mean [SD] number of ER visits</td>
</tr>
<tr>
<td>Mean [SD] number of visits per user</td>
</tr>
<tr>
<td><strong>Injections, MS treatment drugs</strong></td>
</tr>
<tr>
<td>Patients with any injections % (n)</td>
</tr>
<tr>
<td>Mean [SD] number of injections</td>
</tr>
<tr>
<td>Mean [SD] number of injections per user</td>
</tr>
<tr>
<td><strong>Physician visits, all</strong></td>
</tr>
<tr>
<td>Patients with any visit % (n)</td>
</tr>
<tr>
<td>Mean [SD] number of physician visits</td>
</tr>
<tr>
<td>Mean [SD] number of physician visits per user</td>
</tr>
<tr>
<td><strong>Neurologist visits</strong></td>
</tr>
<tr>
<td>Patients with any visit % (n)</td>
</tr>
<tr>
<td>Mean [SD] number of neurologist visits</td>
</tr>
<tr>
<td>Mean [SD] number of neurologist visits per user</td>
</tr>
<tr>
<td><strong>Laboratory</strong></td>
</tr>
<tr>
<td>Patients with any service % (n)</td>
</tr>
<tr>
<td><strong>Radiology</strong></td>
</tr>
<tr>
<td>Patients with any service % (n)</td>
</tr>
<tr>
<td><strong>PT/OT/speech, swallowing</strong></td>
</tr>
<tr>
<td>Patients with any service % (n)</td>
</tr>
<tr>
<td>Mean [SD] number of therapy sessions</td>
</tr>
<tr>
<td>Mean [SD] number of therapy sessions per user</td>
</tr>
</tbody>
</table>

aBoth cohorts excluded patients with any comorbidities, identified using the Charlson Comorbidity Index, measured using any diagnosis code on the claim during the 12 months prior to the index date.
bP value for Fisher’s exact test for proportions and Wilcoxon rank-sum (also known as Mann-Whitney U) test for continuous variables, comparing the MS patient and healthy comparison cohorts.
cIndicates only MS injections identified using HCPCS codes on medical claims.
d1.8% had a medical claim with a HCPCS code for an injectable MS treatment drug. For 1.4%, this represented their only use of injectable MS treatment drugs, i.e., they had no pharmacy claims for an MS injectable.

Results
A total of 1,411 MS patients and 7,055 “healthy comparison” group enrollees met all sample selection criteria (Figure 1). In both groups, 65.6% of the study sample was female (Table 2). Mean ages were 43 years for MS patients and 44 years for “healthy comparison” group enrollees; 68.0% of enrollees in each cohort were the primary insured, 23.1% were spouses, and 8.9% were dependents.

In this sample, 30.8% of MS patients filled prescriptions for MS treatment drugs, and another 1.4% did not have a pharmacy claim for an MS treatment drug but did have it

nonparametric Wilcoxon rank-sum test to account for non-normality.

Results
A total of 1,411 MS patients and 7,055 “healthy comparison” group enrollees met all sample selection criteria (Figure 1). In both groups, 65.6% of the study sample was female (Table 2). Mean ages were 43 years for MS patients and 44 years for “healthy comparison” group enrollees; 68.0% of enrollees in each cohort were the primary insured, 23.1% were spouses, and 8.9% were dependents.

In this sample, 30.8% of MS patients filled prescriptions for MS treatment drugs, and another 1.4% did not have a pharmacy claim for an MS treatment drug but did have it administered in a physician’s office or ER (Table 3). Thus, a total of 32.2% received an injectable MS treatment drug during the year of follow-up. These patients had an average of 7.5 pharmacy claims. In all drug categories examined, the MS patient cohort had significantly ($P < 0.001$) higher use than the “healthy comparison” cohort. This was particularly noteworthy when comparing use of anticonvulsants (21.2% with MS group vs. 3.4% among “healthy comparison” enrollees, $P < 0.001$), antidepressants (33.1% with MS group vs. 14.6% among “healthy comparison” enrollees, $P < 0.001$), antipsychotics (2.4% with MS group vs. 0.6% among “healthy comparison” enrollees, $P < 0.001$), and amphetamines (7.3% with MS group vs. 1.2% among “healthy comparison” enrollees, $P < 0.001$). Among users of anticonvulsants, MS patients had a mean of
therapy (23.7% vs. 9.9%, \( P < 0.001 \); Table 4). MS patients averaged more than 8 physician office visits, and of those seeing a neurologist, the mean number of neurologist visits was 3.4. Only 1.8% of MS patients received injections for MS treatment in an outpatient (or ER) setting; they had a mean of 8.0 such injections during the year. MS patients who received physical therapy had a mean of 20.5 therapy sessions.

The total all-cause health care costs for MS patients over a 12 month post-index period were 4.7 times the costs for “healthy comparison” patients ($18,829 vs. $4,038, \( P < 0.001 \)) and were significantly higher in every category of utilization (Table 5). MS patients had 7.5 times the pharmacy costs ($6,151 vs. $817, \( P < 0.001 \)), nearly 5 times the inpatient cost.

### TABLE 5
Mean Health Care Expenditures in 12-Month Post-Index Period

<table>
<thead>
<tr>
<th>Health Care Expenditures by Service Category</th>
<th>MS Patients(^a) n = 1,411 Mean [SD] Dollars</th>
<th>Healthy Comparison(^a) Cohort n = 7,055 Mean [SD] Dollars</th>
<th>( P ) Value(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inpatient services</td>
<td>4,110 [19,673]</td>
<td>836 [6,929]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MS diagnosis on claim(^c)</td>
<td>1,802 [12,846]</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Emergency room services</td>
<td>432 [1,290]</td>
<td>189 [850]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MS diagnosis on claim(^c)</td>
<td>53 [354]</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Injections, MS drugs(^d)</td>
<td>137 [1,605]</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>MS diagnosis on claim(^c)</td>
<td>265 [366]</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Neurologist visits</td>
<td>615 [4,244]</td>
<td>4 [39]</td>
<td>&lt;0.001</td>
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<tr>
<td>MS diagnosis on claim(^c)</td>
<td>153 [297]</td>
<td>—</td>
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<tr>
<td>Laboratory services</td>
<td>409 [990]</td>
<td>140 [348]</td>
<td>&lt;0.001</td>
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<tr>
<td>MS diagnosis on claim(^c)</td>
<td>82 [318]</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Radiology services</td>
<td>1,693 [3,801]</td>
<td>259 [1,326]</td>
<td>&lt;0.001</td>
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<td>MS diagnosis on claim(^c)</td>
<td>705 [1,720]</td>
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<td></td>
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<tr>
<td>PT/OT/speech, swallowing</td>
<td>295 [1,019]</td>
<td>81 [487]</td>
<td>&lt;0.001</td>
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<td>MS diagnosis on claim(^c)</td>
<td>75 [602]</td>
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<tr>
<td>Other outpatient services</td>
<td>4,753 [11,209]</td>
<td>1,404 [5,003]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MS diagnosis on claim(^c)</td>
<td>1,285 [4,213]</td>
<td>—</td>
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<tr>
<td>Outpatient pharmacy</td>
<td>6,151 [8,574]</td>
<td>817 [1,700]</td>
<td>&lt;0.001</td>
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<tr>
<td>MS drugs(^e)</td>
<td>4,436 [7,828]</td>
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<td></td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>165 [701]</td>
<td>29 [309]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>194 [479]</td>
<td>82 [314]</td>
<td>&lt;0.001</td>
</tr>
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<td>Antipsychotics</td>
<td>24 [253]</td>
<td>6 [132]</td>
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<td>Urinary antibiotics</td>
<td>3 [23]</td>
<td>1 [7]</td>
<td>&lt;0.001</td>
</tr>
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<td>Amphetamines</td>
<td>81 [444]</td>
<td>8 [111]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Adrenals</td>
<td>24 [144]</td>
<td>12 [107]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Other</td>
<td>1,225 [3,070]</td>
<td>679 [1,492]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total</td>
<td>18,829 [28,973]</td>
<td>4,038 [10,588]</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

\( a \) Both cohorts excluded patients with any comorbidities, identified using the Charlson Comorbidity Index, measured using any diagnosis code on the claim during the 12 months prior to the index date.

\( b \) \( P \) value for Wilcoxon rank-sum (also known as Mann-Whitney U) test, comparing the MS patient and healthy comparison cohorts.

\( c \) Indicates a claim with an MS diagnosis in any field—up to 15 fields on an inpatient claim and up to 2 fields on an outpatient claim.

\( d \) Indicates an MS drug reported using a HCPCS code on a medical claim.

\( e \) Indicates a pharmacy claim with an NDC number for an MS drug.

\( f \) Sum of (a) medical claims with MS diagnosis plus (b) medical claims for MS injections plus (c) pharmacy claims for MS drugs.

HCPCS = Healthcare Common Procedure Coding System; MS = multiple sclerosis; NDC = national drug code; OT = occupational therapy; PT = physical therapy; SD = standard deviation.

5.7 pharmacy claims. For antidepressants, the mean was 6.3, for antipsychotics it was 3.7, and for amphetamines it was 4.0. Among MS patients, 25.4% filled a prescription for an adenal medication compared with 10.0% (\( P < 0.001 \)) for the “healthy comparison” enrollees. This category includes prednisone, commonly used in treating acute symptoms of MS.

MS patients were 3.5 times as likely as their “healthy comparison” counterparts to be hospitalized (15.2% vs. 4.3%, \( P < 0.001 \)), 2.1 times as likely to have an ER visit (25.5% vs. 12.2%, \( P < 0.001 \)), and more likely to have physician office visits (95.6% vs. 78.9%, \( P < 0.001 \)), neurologist visits (51.0% vs. 1.5%, \( P < 0.001 \)), laboratory tests (80.8% vs. 61.8%, \( P < 0.001 \)), radiology services (78.4% vs. 46.8%, \( P < 0.001 \)) and physical therapy (23.7% vs. 9.9%, \( P < 0.001 \); Table 4). MS patients averaged more than 8 physician office visits, and of those seeing a neurologist, the mean number of neurologist visits was 3.4. Only 1.8% of MS patients received injections for MS treatment in an outpatient (or ER) setting; they had a mean of 8.0 such injections during the year. MS patients who received physical therapy had a mean of 20.5 therapy sessions.

The total all-cause health care costs for MS patients over a 12 month post-index period were 4.7 times the costs for “healthy comparison” patients ($18,829 vs. $4,038, \( P < 0.001 \)) and were significantly higher in every category of utilization (Table 5). MS patients had 7.5 times the pharmacy costs ($6,151 vs. $817, \( P < 0.001 \)), nearly 5 times the inpatient cost.
($4,110 vs. $836, P < 0.001), and 6.5 times the radiology cost ($1,693 vs. $259, P < 0.001).

The mean pharmacy cost for MS treatment drugs was $4,436, 72% of the total pharmacy cost. Of the $4,110 mean inpatient cost for MS patients, only $1,802 had an MS diagnosis on the claim. Similar patterns were found for other service utilization. Overall, the mean cost associated with MS treatment drugs or claims with an MS diagnosis was $8,839, representing less than one-half (46.9%) of the overall total costs. The remaining $9,990 (33.1% of the total costs), seemingly unrelated to MS, still represented 2.5 times the total mean cost for the comparison group enrollees (P < 0.001).

Discussion

To the best of our knowledge, this is the first such study to assess the direct health care costs and utilization among newly diagnosed MS patients. To report on the direct health care costs and utilization in newly diagnosed patients with MS, we undertook a retrospective analysis of medical and pharmacy claims data among a cohort of newly diagnosed MS patients matched against a “healthy comparison” group. The results of this study provide evidence of the significant burden of early MS on the health care system. The total costs for newly diagnosed MS patients were found to be 4.7-fold ($18,829 vs. $4,038, P < 0.001) that of “healthy comparison” enrollees during a 12 month post-index period. Like many other chronic, systemic illnesses, there was a large additional cost of services beyond MS treatment that could not be related to MS by a diagnosis code.

Prescott et al. (2007) examined costs for all MS patients in 2004 with at least 1 diagnosis for MS or at least 1 prescription for an MS treatment drug using a large U.S. claims database but did not evaluate newly diagnosed MS patients exclusively. They found that the mean annual direct MS-related medical cost was approximately $13,000 (in 2004 dollars). This was much higher than our mean of $8,839. However, Prescott et al. aggregated costs by Episode Treatment Grouper software, a much more liberal definition of MS-related than used in this study where each specific claim had to include an MS diagnosis code. They also included all patients with MS activity as opposed to this study of apparent newly diagnosed cases, and required only 1 diagnosis of MS without prescription of MS drug as opposed to this study which required 2 diagnosis codes in the absence of an MS treatment drug prescription. Prescott et al. reported that 58% filled a prescription for an MS treatment drug, compared with 31% in the present study. The Prescott et al. study also found that 61% of the MS-related cost of care was attributable to the cost of MS injectable pharmacy claims, as compared with one-half ($4,436 of $8,839) in the present study. This discrepancy might be explained by the difference in samples.

Pope et al. (2002) determined the direct all-cause medical costs of MS patients in insured populations. Study data were administrative claims from commercial insurers for 1994 and 1995, Medicare for 1996 and 1997, and Medicaid disabled populations for 1991 through to 1996 from 6 U.S. states. They found that the annual insured expenditures were $7,677 per commercially insured enrollee with MS versus $2,394 for all commercially insured enrollees. They concluded that insured enrollees with MS are 2 to 3 times more expensive than average insured enrollees. We found that the total all-cause health care costs for patients with MS were nearly 5 times those of healthy comparison enrollees. One explanation for the larger disparity in our study is that we excluded enrollees with major comorbid illness from the sample. This, in turn, would certainly impact the comparability of our study with that of Pope et al. The Pope et al. study compared MS patients to overall averages for the insured population, which includes high-cost patients with other health conditions.

O’Brien et al. (2003) estimated the cost of managing an episode of relapse in MS in the United States in terms of the utilization of inpatient resource use and costs derived from 5 states. They found that the average cost per person for high management level episode was $12,870 and that hospital care comprised 71% of the costs. O’Brien et al. also found that the typical cost per moderate episode was $1,847 and a mild episode amounted to $243. Although we did not assess the cost of MS relapses specifically, such relapses may be the driver for the cost differences in hospitalizations between early MS patients and “healthy comparison” patients.

One strength of the present study is that we used a large U.S. administrative claims database (commercial). The group studied was geographically diverse and has included participants with a variety of insurance coverage. We used a full year of history to check for prior MS diagnosis or treatment. This full year of historical claims also creates a good picture of comorbidities. Many studies look at shorter periods of history, which increases sample size at the cost of integrity of the study population. Our use of matching criteria controlled for several demographic factors and comorbidities that are included in the CCI. Our study also benefits from a large sample size of 1,411 MS patients with 5 comparison group cases per patient. The disease definitions for MS were conservative in the sense that 2 claims with MS diagnoses were required for MS (or 1 prescription for an MS treatment drug). Other studies have used only 1 claim. Lastly, by studying newly diagnosed MS patients, we focused on a group that has been neglected in the literature in terms of utilization and cost.

Approximately 32% of MS patients in our study used an MS disease-modifying agent (DMA) in this study, with most of these filling a prescription for a DMA (30.8%) and an additional 1.4% who received a DMA at an outpatient or ER visit yet filled
no prescriptions for a DMA. This is considerably lower than found in other studies such as the North American Research Committee on Multiple Sclerosis (NARCOMS) registry where, in 2001, 45%-50% of relapsing patients were using a DMA.\(^1\) By 2004, use in the NARCOMS registry increased to approximately 55%-65%.\(^1\) Prescott et al. found that 58% of patients with MS activity filled at least 1 prescription for a DMA in 2004. However, a study by Ozminkowski et al. (2004) utilizing the Medstat dataset reported that only 41.2% of patients were treated with a DMA in the year 2000.\(^1\) Furthermore, it is important to note that none of these studies evaluated newly diagnosed MS patients.

**Limitations**

The foremost limitation is the exclusion of enrollees with comorbidities, which keeps the focus on the impact of the newly diagnosed MS, but does not reflect the overall group of newly diagnosed MS cases. Second, data from administrative claims databases have intrinsic potential sources of bias. Information that would affect study outcomes such as explicit measures of clinical and disease severity or socioeconomic status are not readily available. Also, the pharmacy utilization data do not include use of over-the-counter (OTC) medications, and expenditures will not include use of complementary or alternative therapies such as chiropractic or acupuncture. However, in the context of the large health care expenses of MS patients, OTC medications and complementary or alternative therapies are unlikely to substantially alter the cost picture. Third, chart review or independent confirmation of coding was not possible. Fourth, the study population was drawn from a sample of individuals and their dependents with employer-sponsored health insurance. As such, the findings from this study may not be generalizable to the entire U.S. population, particularly individuals who are covered under Medicare or Medicaid. Fifth, this study examines patients who have been recently diagnosed with no comorbidities and will not reflect the utilization patterns and costs of patients with long-term or established disease, or with comorbid conditions. Sixth, using 1 year of historical claims data to identify people with no prior diagnosis of MS will inevitably include some patients who were diagnosed more than 12 months prior but had no MS care in the preceding 12 months. Seventh, although 53.1% of the higher utilization and costs for MS patients compared with healthy enrollees could not be directly attributed to an MS diagnosis, it is clear that patients with MS incur higher costs than enrollees without, when both groups are pre-screened to remove patients with comorbidities. MS patients were help-seeking and required to have both insurance coverage and at least 2 encounters with the health care system that were related to their condition, or 1 prescription for an injectable MS treatment drug. Eighth, excluding comorbidity is possible only to the extent that comorbid diagnoses are coded on medical claims. Ninth, we analyzed claims data from the 3-year period 2004 through 2006, and pharmacy-medical benefits have changed over time.

**Conclusions**

Newly diagnosed MS patients have significantly higher rates of hospitalizations, radiology services, and ER and outpatient visits compared with non-MS “healthy comparison” patients. MS presents a considerable burden to the U.S. health care system within the first year of diagnosis.

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**DISCLOSURES**

This study was funded by sanofi-aventis. U.S. Jhaveri is an employee of sanofi-aventis. Chung is a fellow of Rutgers University. Asche, Singer, and Miller are consultants to sanofi-aventis.

Concept and design and data interpretation were performed by Asche, Jhaveri, Miller, and Singer. Data collection was performed by Asche, Chung, Jhaveri, and Singer. The manuscript was written by Asche, with the assistance of Singer, Jhaveri, and Miller, and revised by Asche, with the assistance of Singer and Jhaveri.

**REFERENCES**

### Drug Categories and Drugs

<table>
<thead>
<tr>
<th>Drug Category</th>
<th>Therapeutic Drug Class</th>
<th>Generic Drug Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenals</td>
<td>166</td>
<td>Beclomethasone, Betamethasone, Budesonide, Cortisone, Desoxycorticosterone, Dexamethasone, Fluodrocortisone, Flumisolide, Fluticasone (and combinations), Hydrocortisone, Methylprednisolone, Mometasone Furoate, Prednisolone, Prednisone, Triamcinolone</td>
</tr>
<tr>
<td>Amphetamines</td>
<td>71</td>
<td>Amphetamine, Benzphetamine, Dexmethylphenidate, Dextroamphetamine, Diethylpropion, Lisdexamfetamine, Methamphetamine, Methylphenidate, Modafinil, Phendimetrazine, Phenetermine</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>64-68</td>
<td>Carbamazepine, Clonazepam, Divalproex, Ethosuximide, Felbamate, Gabapentin, Lamotrigine, Levetiracetam, Magnesium, Methsuximide, Oxcarbazepine, Phenytoin, Primidone, Tiagabine, Topiramate, Valproic Acid, Zonisamide</td>
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<td>Antidepressants</td>
<td>69</td>
<td>Amtriptyline (and combinations), Amoxapine, Bupropion, Citalopram, Clomipramine, Desipramine, Doxepin, Duloxetine, Escitalopram, Fluoxetine, Fluvoxamine, Imipramine, Maprotiline, Mirtazapine, Nefazodone, Nortriptyline, Paroxetine, Phenelzine, Protriptyline, Sertraline, Tranylcypromine, Trazadone, Trimipramine, Venlafaxine</td>
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<td>Antipsychotics</td>
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<td>Aripiprazole, Chlorpromazine, Clozapine, Fluphenazine, Haloperidol, Loxapine, Olanzapine, Paliperidone, Perphenazine, Pimozide, Quetiapine, Risperidone, Thioridazine, Thiothixene, Trifluoperazine, Ziprasidone</td>
</tr>
<tr>
<td>Urinary antibiotics</td>
<td>19</td>
<td>Belladonna, Fosfomycin, Methenamine (and combinations), Nitrofurantoin</td>
</tr>
</tbody>
</table>


Multiple sclerosis (MS) affects approximately 400,000 Americans. Most patients are diagnosed between 20 and 50 years of age, and the disease develops in twice as many women as men. MS is characterized by scattered areas of inflammation, demyelination, and axonal injury affecting the brain, optic nerves, and spinal cord. Inflammatory demyelination can be accompanied by clinical symptoms, termed relapses, followed by some degree of recovery, producing the classic relapsing-remitting MS (RRMS) seen early in the disease. Secondary progressive MS (SPMS) occurs when persistent signs of central nervous system (CNS) dysfunction develop after a relapse, and the disease progresses between relapses. RRMS develops into secondary progressive MS in 50% of patients within 10 years and 75% of patients within 25 years. Primary progressive MS (PPMS) occurs when the clinical course is gradually progressive and is the diagnosis in approximately 20% of MS cases. Clinical course and disability vary between patients and depend on MS disease type.

The medical and pharmacy costs of MS are substantial. Pope et al. (2002) analyzed the cost of MS in beneficiaries with private insurance, Medicare, or Medicaid. Excluding prescription drug costs from all comparisons because Part D coverage was not in effect at the time of the study, members with MS enrolled in private insurance had 3 times the average all-cause medical expenditures compared with non-MS members ($6,329 vs. $2,001). Medicare members with MS had double the medical expenditures compared with members without MS ($13,048 vs. $6,006). Finally, members with MS covered by Medicaid had 2.5 times the medical costs compared with members without MS ($10,358 vs. $4,111). In the private insurance and Medicaid cohorts, prescription drug costs were also higher in the MS group.

Using survey data and estimated costs for a random sample of participants in the North American Research Committee on MS (NARCOMS) patient registry who reported use of 1 or more of the 4 MS biologic agents, Kobelt et al. (2006) estimated that the total mean annual direct (inpatient and outpatient services, prescriptions) and indirect costs (loss of productivity, work loss or reduction) of MS were $47,215 per patient (in 2004 dollars). Direct medical and nonmedical costs including “informal care from family and friends” accounted for $29,634 per patient per year (PYPY). The single largest expenditure in the direct cost category was MS biologics at $16,050 PYPY or 34.0% of the overall direct and indirect costs. Price inflation for existing drugs and the introduction of new agents for MS promise to further increase the cost of MS and present a growing challenge for payers.

In this issue of JMCP, Asche et al. analyze the all-cause health care utilization and costs for patients newly diagnosed with MS or with at least 1 claim for an injectable drug for MS. The study involved an analysis of the Medstat MarketScan Commercial Claims and Encounters database composed of approximately 8 million beneficiaries from 45 U.S. commercial health plans. The study compared 1,411 patients with MS with 7,055 healthy subjects without MS. The analysis found that patients with MS were 2 times as likely to visit the ER, 1.2 times as likely to visit the doctor's office, and 2.4 times as likely to have physical, occupational, or speech therapy compared with patients without MS. These increases in utilization of health care created a significant difference in 12-month direct health care costs: $18,829 for MS patients compared with $4,038 for patients without MS. Pharmacy costs per member were 7.5 times as high in patients with MS compared with patients without MS ($6,151 vs. $817).

The analysis by Asche et al. has limitations in understanding the cost impact of biologics for MS. First, only 30.8% of MS patients in the sample received treatment with MS biologics, compared with 100% of the MS patients in the NARCOMS study by Kobelt et al. The difference in utilization of biologic agents explains some of the disparity in PYPY pharmacy expenditures on MS biologics between NARCOMS ($16,050) and Asche et al. ($4,436), despite older data (from 2004) in the NARCOMS study. Second, the analysis by Asche et al. spanned the period from 2004 through 2006, and the arrival of new agents and continued price inflation are complicating factors. However, the authors did adjust the costs to 2010 dollars to give a current picture of the costs of therapy.

Kunze et al. published an analysis of cost trends and utilization of MS agents for the time period 2004 through 2007. The study involved 9 million commercially insured members and the 4 self-injectable MS biologic agents: glatiramer, interferon (IFN) beta-1a subcutaneous (SC), IFN beta-1b SC, and IFN beta-1b intramuscular (IM). Claims for MS biologics ranged between 82 and 83 claims per 100,000 members during the 45-month study period. However, spending for MS biologics increased from 1.8% of total pharmacy spending in 2004...
Price Increases and New Drugs Drive Increased Expenditures for Multiple Sclerosis

<table>
<thead>
<tr>
<th>Year</th>
<th>N</th>
<th>Total Medical Expenditures</th>
<th>Total Pharmacy Expenditures</th>
<th>% Pharmacy</th>
<th>Pharmacy Expenditure Trend Compared with Previous Year</th>
<th>CAGR</th>
<th>Medical Expenditure Trend Compared with Previous Year</th>
<th>CAGR</th>
<th>Combined (Medical and Pharmacy) Compared with Previous Year</th>
<th>CAGR</th>
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<td>$4,460,924</td>
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</tr>
<tr>
<td>2009</td>
<td>361</td>
<td>$2,974,376</td>
<td>$15,577</td>
<td>6.3%</td>
<td>7.5%</td>
<td>8.2%</td>
<td>$37,592</td>
<td>10.4%</td>
<td>$37,592</td>
<td>10.4%</td>
</tr>
</tbody>
</table>

aData are from a commercial midwestern health plan of approximately 1.4 million members. The analysis period was January 1, 2006, through September 30, 2010. 

Benchmark Analysis of Medical and Pharmacy Costs for Commercial Health Plan Members with MS

In order to understand the total cost of care trend among individuals with MS, we analyzed medical and pharmacy administrative pharmacy claims to identify a cohort and then followed the cohort for 4 years. This MS cohort was identified through an analysis of pharmacy and medical claims data for approximately 1.4 million commercial health plan members for the period from 2006 through 2009 to examine the total costs and rate of cost increase for MS management. In this midwestern commercial health plan, 390,108 members were continuously enrolled for the 4-year period. Members eligible for analysis were required to have been continuously enrolled for the 4-year duration, and meet at least 1 of 2 criteria: (a) at least 1 medical claim with an MS-related International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis code of 340 in January 2006 and in each subsequent year (2007, 2008, and 2009); or (b) at least 1 MS medical claim in the first quarter of 2006 and a pharmacy claim for an MS drug (Generic Product Identifier [GPI, Wolters Kluwer Health, Indianapolis, IN] codes: 62400030102120, 62400030106420, 62403060452020, 62403060452040, 62403060452060, 62403060456420, 62403060456430, 62403060502120, 62405050001320, 62406030007420, 62407025100120) in January 2006. Costs were total allowed amounts (plan and member) for all medical and pharmacy claims. A total of 361 patients met analytic criteria. Medical costs (without pharmacy) increased by 24.3% from $12,535 PPPY in 2006 to $15,577 in 2009 (Table 1). Combined medical and pharmacy costs increased by nearly 27% from $29,652 PPPY in 2006 to $37,592 (Table 1). The cost trends presented here are for a fixed cohort followed over time and may be confounded by worsening disease resulting in increased medical and pharmacy expenditures. However, pharmacy biologic expenditures are unlikely to be influenced by worsening disease as combination biologic therapy is not approved by the U.S. Food and Drug Administration (FDA).

Price inflation has led to an increasing cost burden on patients as well. An analysis of internal data from our 2006 to 2010 commercial book of business of approximately 9.0 million members indicates that mean member out-of-pocket cost share per prescription claim for MS therapies nearly doubled from 2006 to 2009 (Table 2). Prescription claims in the analysis of cost per prescription were adjusted by days supply (0-34 days = 1 claim, 35-68 days = 2 claims, 69-120 days = 3 claims). These data support the findings of Asche et al. and Kunze et al. regarding the growing medical and pharmacy costs of MS.

Cost-Effectiveness of MS Biologics

The cost-effectiveness of the MS biologics has been analyzed in previous studies in JMCP with conflicting results. Goldberg et al. (2009) analyzed the 2-year cost effectiveness for the 4 agents (IFNs and glatiramer) when used first-line for RRMS. The estimated costs per relapse avoided were $80,589, $87,061, $88,310, and $141,721 for IFN beta-1a SC, IFN beta-1b SC, glatiramer, and IFN beta-1a IM, respectively. Alternatively, Bell et al. (2007) used a Markov model to estimate the cost per quality-adjusted life year (QALY) gained for the 4 self-administered MS biologics. In contrast to Goldberg et al., this study found glatiramer to be the most cost-effective at $258,465 per...
QALY. IFN beta-1a IM, IFN beta-1b SC, and IFN beta-1a SC had costs per QALY of $303,968, $310,691, and $416,301, respectively.9 Payers can expect cost-effectiveness of the MS biologics to erode as price inflation continues.

Recent Drug Approvals for MS Enlarge Opportunity for Utilization Management

The pharmacy costs of managing MS are likely to increase further with the approval of new therapies. Dalfampridine was approved by the FDA in January 2010 to improve walking in patients with MS as demonstrated by an increase in walking speed.10 Dalfampridine does not prevent MS relapses; instead, dalfampridine is theorized to exert its effects on walking ability by blocking potassium channels and improving conduction in motor neurons damaged by MS.10 Dalfampridine clinical trials included patients with PPMS and thus may expand the pool of MS patients eligible for treatment with prescription agents. The average wholesale price (AWP) of a 10 mg dalfampridine tablet is $21.12, and 1 month of therapy would cost $1,267.20.11 This cost would be in addition to, rather than replacing, any cost associated with MS biologics pharmacotherapy.

In September 2010, fingolimod was approved by the FDA as the first oral MS agent, with the specific indication to reduce relapses and delay disability progression in patients with relapsing forms of MS.12 The AWP of fingolimod is $158 per capsule or $4,740 per month.11 The cost of fingolimod is significantly higher than those of the competing injectable MS biologics.

MS is a devastating disease, and patients should be managed with approved therapies to reduce relapses and manage disability. However, payers must be prepared to manage the MS category to ensure cost-effective use. MS drug class maturation provides payers with greater opportunities to derive cost savings through tools like formulary, benefit design, and utilization management programs.

Clinical guidelines presently recommend initiating therapy in patients with RRMS using either an IFN or glatiramer, and the guidelines do not prefer one IFN product over another.13,14 Comparative trials have shown a possible advantage in reduced relapse rates with IFN beta-1a SC or IFN beta-1b SC compared with IFN beta-1a IM.15 However, the effect on long-term disability between these agents is unclear.15 Comparative data among IFN beta-1a SC, IFN beta-1b SC, and glatiramer have demonstrated comparable efficacy in reducing relapse rates.15 The similar efficacy and safety of approved therapies presents an opportunity for payers to prefer 1 or 2 agents on the formulary. Payers should ensure the tier differential is substantial enough to encourage use of preferred products and shift market share to formulary agents. Data are limited on MS biologics in other types of MS, and no MS biologic or fingolimod has been shown to be effective in PPMS.

Utilization management programs present another opportunity to promote safe use and control MS costs. Step-therapy programs can require trial of one agent prior to another and may prevent concurrent use of 2 relapse-preventing agents, which has not been evaluated for safety or effectiveness. Patients shown to be intolerant to or failing preferred agents could then be approved for nonpreferred therapies. Prior authorization (PA) programs may be implemented to verify appropriate use of dalfampridine and other MS agents for only types of MS for which there are efficacy and safety data available. Coverage of dalfampridine should be limited to patients with MS and renewed upon demonstration of efficacy. Responder rates in dalfampridine pivotal trials ranged from 35%-43% compared with 8%-9% for placebo.16,17 Response generally occurred quickly and was sustained during the trial.16,17 PA programs

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*Drugs in analysis include dalfampridine, all 3 interferon agents, glatiramer, and natalizumab processed through the pharmacy benefit. Data are from commercial health plans totaling approximately 9.0 million members. The analysis period was January 1, 2006, through September 30, 2010.

Pharmacy claims were adjusted by days supply: 0-34 days = 1 claim, 35-68 days = 2 claims, 69-120 days = 3 claims.

First and third quartiles are 25th and 75th percentiles, respectively (interquartile range).

1 Calendar quarters through September 30, 2010.
claim in 2006 to $82 in 2009 (Table 2). Although the mean per prescription claim for MS agents increased from $48 per prescription, data showed that the mean out-of-pocket patient expenditure per prescription claim is likely the result of prescription abandonment in association with members paying more than $100. The analysis found a significantly higher associated rate of prescription abandonment for MS patients paying more than $200 per prescription compared with patients paying $100 or less. Members paying $100 or less per prescription for MS medications were compared with patients paying more than $100. The analysis found a significantly higher associated rate of prescription abandonment for MS patients paying more than $200 per prescription compared with patients paying $100 or less.

Our benchmark analysis of pharmacy and medical claims data showed that the mean out-of-pocket patient expenditure per prescription claim for MS agents increased from $48 per claim in 2006 to $82 in 2009 (Table 2). Although the mean patient expenditure per prescription appears higher in 2010 than in 2009, the data are through 3 quarters and therefore are not representative of an entire year. Median patient expenditures per prescription are roughly one-half the median expenditure and have risen minimally from $25 in 2006 to $30 in 2009. The discrepancy between mean and median patient expenditure per prescription claim is likely the result of 2 factors. First, Gleason et al. found that 13.8% of patients filing prescriptions for MS biologic drugs paid more than $200 per prescription, and 5.4% paid more than $500 per prescription; these higher costs skew the mean upward relative to the median. Second, members pay higher out-of-pocket amounts early in the year when deductibles have not been met (Table 2). Nonadherence to therapy may increase the risk of relapse and associated disability. Payers should consider setting a maximum out-of-pocket limit of between $100 and $150 per prescription when utilizing a specialty tier for MS biologic agents.

MS is a potentially disabling disease, but treatment options are available. The article by Asche et al. and others like it highlight the escalating costs associated with MS management. Price inflation continues to be the primary driver of increased pharmacy costs for MS patients. Opportunities exist for payers to manage the MS categories and control cost. Preferring select agents on formulary, developing utilization management programs to promote patient safety, and encouraging use of preferred agents and specialty pharmacies all provide opportunities to optimize clinical and service outcomes at the lowest cost.

Benefit Design Considerations and Member Cost Share

Benefit designs including a fourth cost-share tier or specialty cost-share tier are becoming more common. Part of the function of a specialty cost-share tier is to differentiate specialty products and increase cost share to members. However, payers should exercise caution when utilizing a specialty tier and associated increased cost share. Gleason et al. (2009) examined the rate of prescription abandonment in association with member cost share. Members paying $100 or less per prescription for MS medications were compared with patients paying more than $100. The analysis found a significantly higher associated rate of prescription abandonment for MS patients paying more than $200 per prescription compared with patients paying $100 or less.

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Price Increases and New Drugs Drive Increased Expenditures for Multiple Sclerosis


Lessons Learned from Randomized Trials and Recent Experience with Health Information Technology: Promising Interventions Meet Real-World Patient Care

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

“Only when providers enter orders electronically can the computer help improve decisions by applying clinical logic to those choices in light of all the recorded patient data.”—Federal officials David Blumenthal and Marilyn Tavenner, commenting on “meaningful use” incentives in the Health Information Technology for Economic and Clinical Health Act.1

“I was ordering Cortisporin, and Cortisporin solution and suspension comes up. The patient was talking to me, I accidentally put down solution, realized that’s not what I wanted. … I would not have made that mistake, or potential mistake, if I had been writing it out because I would have put down what I wanted.”—U.S. physician, commenting in a 2003 interview on experiences in using a computerized prescription order entry system.2

In a 2010 commentary on the occasionally large gaps between the aspirations of researchers and the reality of study results, biostatistician Andrew Vickers recounted the frustrating experience of British statisticians who were trying to determine better ways to set and explode depth charges as countermeasures against German U-boats that were sinking supply convoys during World War II.3 After months of working with data on “the direction in which the depth charge had been fired relative to the direction of the ship and then whether the submarine had been hit,” the statisticians “had gotten precisely nowhere in working out how best to target depth charges”—that is, until one brave analyst volunteered to go to sea and observe field conditions firsthand. Direct observation showed the statistician that battlefield winds made the firing data with which he had been working “totally unreliable.” After the statistician wisely “[ignored] most of the data that he’d been sent” and performed a reanalysis using revised assumptions, battlefield tactics were adjusted successfully.3

A recently published randomized controlled trial (RCT) of a popular health care intervention provides a potent reminder that real-world experience and rigorous tests of our suppositions can and often do produce challenges to conventional wisdom. Like the failure of statistical models based on erroneous battlefield data to produce accurate predictors of depth charge “hits,” these challenges can—and should—lead to rethinking about how “field conditions” in health care affect the outcomes of managed care interventions.

**Decision Support in Inpatient CPOE Takes a HIT in Rigorous Testing**

An RCT reported by Strom et al. in September 2010 assessed the effects of a computerized prescription order entry (CPOE) decision support feature that put a “nearly hard stop” on concomitant orders for warfarin and trimethoprim-sulfamethoxazole (TMP/Sulfa) in 2 academic medical centers from August 2006 to February 2007.4 The rationale for conducting the trial was sensible—the vast majority of real-time alerts to drug interactions or potential adverse drug events (ADEs) are overridden by prescribers,5 raising the possibility that a “hard stop” on prescribing contraindicated drug-drug combinations would improve patient safety.

The intervention consisted of a pop-up window on the CPOE display notifying the clinician that “the prescription of warfarin and TMP/Sulfa together is completely prohibited except in cases of urgent need for the TMP/Sulfa.” The warning message advised the prescriber to either discontinue TMP/Sulfa to permit the prescribing of warfarin or to contact the pharmacy if the patient had “an urgent need” for TMP/Sulfa. The only automated method to override the alert was to enter the indication of *Pneumocystis carinii* pneumonia prophylaxis into the order, and to respond affirmatively when asked “Dr. xxx, you have certified that this patient has PCP. Click on ‘Acknowledge’ button to certify that this diagnosis is still active xxx, you have certified that this patient has PCP. Click on ‘Acknowledge’ button to certify that this diagnosis is still active xxx, you have certified that this patient has PCP. Click on ‘Acknowledge’ button to certify that this diagnosis is still active xxx, you have certified that this patient has PCP. Click on ‘Acknowledge’ button to certify that this diagnosis is still active xxx, you have certified that this patient has PCP. Click on ‘Acknowledge’ button to certify that this diagnosis is still active xxx, you have certified that this patient has PCP. Click on ‘Acknowledge’ button to certify that this diagnosis is still active xxx, you have certified that this patient has PCP. Click on ‘Acknowledge’ button to certify that this diagnosis is still active xxx, you have certified that this patient has PCP. Click on ‘Acknowledge’ button to certify that this diagnosis is still active xxx, you have certified that this patient has PCP. Click on ‘Acknowledge’ button to certify that this diagnosis is still active xxx, you have certified that this patient has PCP. Click on ‘Acknowledge’ button to certify that this diagnosis is still active xxx, you have certified that this patient has PCP. Click on ‘Acknowledge’ button to certify that this diagnosis is still active xxx, you have certified that this patient has PCP. Click on ‘Acknowledge’ button to certify that this diagnosis is still active xxx, you have certified that this patient has PCP. Click on ‘Acknowledge’ button to certify that this diagnosis is still active xxx, you have certified that this patient has PCP. Click on ‘Acknowledge’ button to certify that this diagnosis is still active xxx, you have certified that this patient has PCP. Click on ‘Acknowledge’ button to certify that this diagnosis is still active xxx, you have certified that this patient has PCP. Click on ‘Acknowledge’ button to certify that this diagnosis is still active xxx, you have certified that this patient has PCP. Click on ‘Acknowledge’ button to certify that this diagnosis is still active xxx, you have certified that this patient has PCP. Click on ‘Acknowledge’ button to certify that this diagnosis is still active xxx, you have certified that this patient has PCP. Click on ‘Acknowledge’ button to certify that this diagnosis is still active xxx, you have certified that this patient has PCP. Click on ‘Acknowledge’ button to certify that this diagnosis is still active xxx, you have certified that…”

For the sample overall, the intervention was “extremely effective” at reducing the co-prescribing of warfarin with TMP/Sulfa. The rates of “desired responses,” defined as “not re-ordering the alert-triggering drug within 10 minutes” of the “firing” of the alert (or silent “firing” in the control group), were 57.2% (111 of 194 alerts) for the intervention group versus 13.5% (20 of 148) for the control group (adjusted odds ratio = 0.12, 95% confidence interval [CI] = 0.045-0.33). However, the trial was halted early by the study’s Institutional Review Board (IRB) for ethical reasons after 4 intervention group patients “who needed immediate drug therapy” experienced “clinically important treatment delays” that were either definitely (n = 4) or probably (n = 2) “related to” the intervention—a 1-day delay in warfarin administration, a 3-day delay in warfarin initiation for a patient...
who received alternative anticoagulation, a “failure to prescribe appropriate [TMP/Sulfa] prophylaxis for an otherwise critically ill patient,” and a 3-day delay in “initiation of antibiotic therapy recommended by the Infectious Diseases Consultation Service.” The IRB’s decision to terminate the study because of potential harm to the intervention group is especially notable because in the study’s initial planning stages, the IRB had expressed ethical concerns about “depriving” the control group of the patient safety intervention.4

Strom et al. concluded that the unexpected outcome of their study “emphasizes the need for formal evaluation and monitoring of programmatic interventions rather than simply assuming that they will be effective.”4 In a subsequent interview with Reuters Health, Strom pointed to the study results as a “dramatic example” of the need to “study the side effects of these [CPOE decision support] interventions” prior to widespread implementation.6

**HIT and CPOE: What Does “Meaningful Use” Mean for Health Care Providers?**

The findings by Strom et al. take on special importance in light of recent public policy developments related to health information technology (HIT), including the July 2010 announcement by the Centers for Medicare & Medicaid Services (CMS) of regulations to be enacted pursuant to the Health Information Technology for Economic and Clinical Health (HITECH) Act, a portion of the American Recovery and Reinvestment Act (ARRA) passed in February 2009.7,8 Of the approximately $48.8 billion provided in the ARRA to encourage the development and adoption of HIT,9 “up to $27 billion”1 was allocated for incentive payments to Medicare and Medicaid providers that implement “meaningful use” of electronic health records (EHRs).8

The rationale underlying meaningful use criteria, as described in a CMS summary, is that “[b]y implementing and meaningfully using an EHR system, providers will reap benefits beyond financial incentives—such as reductions in errors, availability of records and data, reminders and alerts, clinical decision support, and e-Prescribing/refill automation.”8 Meaningful use will be defined by CMS in stages, with Stage 1 in effect in calendar years 2011 and 2012, Stage 2 estimated in 2013, and Stage 3 estimated in 2015.8 Beginning at Stage 3, providers that are “not meaningful users of EHR technology” will incur Medicare “payment adjustments” (financial penalties).10 Specific criteria for Stages 2 and 3 have not yet been announced by CMS but will “continue to expand on” the “baseline” criteria used at Stage 1.8

During Stage 1, qualification for incentive payments will require meeting 20 of 25 meaningful use criteria, of which 15 are mandatory “core objectives” intended to represent “basic functions that enable EHRs to support improved health care” (Table 1).1 Of the 15 core objectives, 5 pertain to medication management activities. In addition to standards for data recording and transmission for 30%-80% of patients, depending on the specific patient care activity, core requirements address infrastructure necessary to meet future requirements, such as the implementation of at least 1 clinical decision support tool.1,11 The decision support tools are notable because, as envisioned by U.S. Department of Health and Human Services (DHHS) and CMS, they reflect “the capability that undergirds much of the value of EHRs: using records to enter clinical orders and, in particular, medication prescriptions.”1

Despite popular press attributions of HIT incentives to the current Presidential administration,9 enthusiasm for the anticipated effects of “meaningful use” of HIT on patient outcomes, especially safety, is neither new nor politically partisan. In the much-cited 1999 report, To Err Is Human: Building a Safer Health System, the Institute of Medicine identified “automated medication order entry” as a “known [system] for improving safety” that was being underutilized by hospitals.12 The increased use

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**TABLE 1** Summary of “Core Objectives” for “Meaningful Use” of EHRs

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<th>Core Objective</th>
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<tr>
<td>• Electronic recording of demographic data, vital signs, smoking status, and “chart changes” (e.g., childhood growth chart recordings)—more than 50% of patients</td>
</tr>
<tr>
<td>• At least 1 entry for (a) an “up-to-date problem list of current and active diagnoses,” (b) active medication list, and (c) active medication allergy list—more than 80% of patients</td>
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<td>• Clinical summary of the provider office visit given to the patient within 3 business days—more than 50% of visits</td>
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<tr>
<td>• Electronic copy of discharge instructions by hospitals and emergency rooms upon request at time of discharge—more than 50% of requesting patients</td>
</tr>
<tr>
<td>• Electronic copy of health information upon request within 3 business days—more than 50% of requesting patients</td>
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</table>
| • Generation and transmission of electronic prescriptions using certified EHR technology (physician offices only)—more than 40% of permissible prescriptions

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BPermissible prescriptions exclude Schedule II controlled substances.**5**

CMS = Centers for Medicare & Medicaid Services; CPOE = computerized prescription order entry; EHR = electronic health record.
of HIT has been enthusiastically promoted by a diverse group that includes former Speaker of the House Newt Gingrich, who proclaimed as early as 2005 that “paper kills” and described the use of paper medical records in the United States as an “utterly irrational national security risk.”13 and President Barack Obama, who declared in a February 2009 address to a joint session of Congress that investment in EHR use would “reduce errors, bring down costs, ensure privacy and save lives.”14 The popular press contribution to the chorus includes a 2009 CNN report claiming that the “first, most obvious cost saving comes from the time EHRs save just from turning them on” because, with an EHR system, “patients don’t need to take the time to explain medical history to new doctors. EHRs help doctors diagnose faster, significantly cut down on the time it takes hospital staff to chart patients’ information and ultimately slash the length of an average patient visit.”15

Exaggerated Cost Savings and Benefits from HIT?
Not all knowledgeable observers agree that HIT represents a longed-for “silver bullet” solution to problems of patient safety and cost in the United States. Critics of providing financial incentives for widespread EHR adoption argue that although computerized records can produce benefits, such as centralization of information and prevention of dispensing errors attributable to illegible handwriting, there is no evidence of economic benefit, let alone the “huge savings”16 asserted by EHR proponents.15,16 In an editorial referring to oft-cited EHR cost savings estimates as an “$80 billion exaggeration,” Harvard Medical School faculty members Groopman and Hartzband accurately observe that these projected savings were based on economic modeling conducted by researchers who chose intentionally to ignore empirical evidence of problems with HIT systems in developing their estimates, a methodological approach that was acknowledged by Hillestad et al. to interpret reported evidence of negative or no effect of HIT as likely being attributable to ineffective or not-yet-effective implementation.17 was foundational for the large size of the cost savings estimates.15 Moreover, in a separate technical document, the investigative group that produced the estimates transparently acknowledged marked limitations in the base of available empirical evidence about HIT: “Out of more than 1,400 screened articles, we were able to extract only 42 findings that could be used as input to our model of national savings.”18 Notably, the only RCT of EHR use in inpatient settings that was available to inform the 2005 theoretical estimates was published in January 1993 and studied one of the first EHRs in use in the United States.18,19

Supplementing limited empirical evidence with expert opinion, Hillestad et al. estimated that 90% adoption of EHRs by providers in a mature system (i.e., in the final year of a 15-year adoption period) could result in an annual $57.1 billion in inpatient cost savings, mostly due to reductions in length of stay ($34.7 billion) and nursing time ($13.7 billion).17 Length-of-stay reductions would accrue because EHR use would reduce “delays in the ordering process, including waiting for written orders to be transcribed and communicated; delays caused by errors, as when a needed test is inadvertently ordered late; delays in task prioritization; delays in ordering ancillary services following nursing assessment, in searching for paper documents before visiting a patient, and in coordinating all of the information and communications necessary for discharge planning.”18 Nursing time would be made more productive because the time that nurses would save on document by using the EHR could instead be spent “[taking] care of additional patients, keeping quality constant.”18

In both the inpatient and outpatient settings, Hillestad et al. estimated efficiency savings attributable to reductions in laboratory test use ($4.6 billion because of “the potential to reduce unnecessary tests by making physicians aware of current [laboratory test] results and by alerting them to new orders that may be superfluous”).18 Estimated savings from using CPOE were $14.5 billion due to “structuring medication selections to align with formulary rules; advising physicians of the cost-benefit characteristics of specific drugs at the time of ordering; recommending less-expensive alternative drugs, including generics; encouraging providers to discontinue unneeded or contraindicated medications; and encouraging timely conversion from intravenous to oral medications.”18 CPOE would enhance patient safety by warning of interactions and reducing errors and, in “the longer term,” would “[provide] the information needed to redesign the order-execution process so that errors become even harder to make.”17

Hillestad et al. estimated that the $77.4 billion in annual savings due to EHR efficiencies could be doubled if HIT were also used to facilitate “interventions intended to keep people healthy (or healthier),” using a series of assumptions that
appearing heroic in retrospect—for example, that EHR-generated reminders could increase compliance with U.S. Preventive Services Task Force recommendations to 100% and that EHR-facilitated identification of patients in need of disease management programs for asthma, congestive heart failure, chronic obstructive pulmonary disease (COPD), and diabetes could result in 100% program participation. By “controlling acute care episodes,” the disease management programs would “greatly reduce hospital use at the cost of increased physician office visits and use of prescription drugs,” generating “potential annual savings of tens of billions of dollars.” Notably, the Hillestad et al. projections were published about 2 years prior to the announcement in 2007 that the Medicare Health Support demonstration project, an RCT of disease management provided to Medicare beneficiaries, had not only failed to yield the hypothesized return-on-investment from savings on inpatient care, but had failed to yield even enough savings to cover vendors’ fees, resulting in termination of the project in 2008.20

**Evidence About the Effects of CPOE on Safety and Costs**

Like the RCT by Strom et al., observational studies of CPOE systems have shown that for the vast majority of prescriptions, CPOE represents an improvement over paper.21-23 For example, Kaushal et al. (2010) used a prospective cohort analysis of prescribing errors in community-based practices, comparing physicians who used paper prescriptions (n = 15 physicians, 3,684 prescriptions) with adopters of a decision-supported CPOE system that included dosing recommendations and checks for allergies, drug-drug interactions, and duplicate therapies (n = 15 physicians, 3,848 prescriptions). Error rates for e-prescribers decreased from 42.5% prior to CPOE adoption to 6.6% at 1 year post-adoptions, compared with baseline and 1-year rates of 37.3% and 38.4%, respectively, in the paper-prescribing group (P < 0.001 comparing 1-year error rates).21 Using a pre-CPOE versus post-CPOE design with multivariate analysis to study prescribing error rates in a community-based multispecialty health care system, Devine et al. (2010) found a significant reduction in prescribing errors from 18.2% of 5,016 handwritten prescriptions to 8.2% of 5,153 computerized prescriptions but no significant reduction in preventable ADEs that caused harm.22

However, underscoring the importance of the study by Strom et al., the potential for CPOE and EHRs to introduce errors—and the resulting effects on safety and cost overall—are understudied in rigorous research. General weakness in the evidence base about CPOE, particularly with respect to its effect on ADE rates, was identified in 2 systematic reviews conducted by Eslami et al., one in inpatient settings (studies published through August 2006) and the other in outpatient settings (studies published through March 2006).24,25 Both reviews identified few randomized trials, and both found inadequate and conflicting evidence about the effects of CPOE on efficiency, health care cost, and patient safety.

**Effects of CPOE in Inpatient Settings**

In the systematic review of CPOE in inpatient settings, 67 studies, including only 8 RCTs, were identified by Eslami et al. Of 4 RCTs in which cost/efficiency was the outcome, 2 produced statistically significant positive effects, 1 produced reports of positive effects with inconsistent reporting of statistical significance, and 1 produced no significant impact.25 Of 22 nonrandomized studies, 18 suggested “a positive effect of CPOE on safety” as measured by prescribing errors. However, no randomized studies of the effect of CPOE on prescribing errors were identified, and there were no studies (using any research design) of ADEs at all.25

More recent observational economic analyses of the use of HIT, including decision-supported CPOE, in “real-world” hospital settings have generally not supported projections of cost savings, often (but not always) finding modestly (usually less than 10%) higher costs associated with EHR use with or without decision-supported CPOE.26-28 However, the base of evidence about the effects of HIT remains remarkably limited. Current (October 2010) PubMed searches limited to RCTs, conducted using combinations of a number of terms (la “hospital” or “inpatient” with [b] “cost” and [c] “electronic health record,” “electronic medical record,” “computerized prescription order entry,” or “CPOE”), yield only 1 RCT of the economic impact of EHRs or CPOE in inpatient settings—the 1993 RCT that was used by Hillestad et al. in their 2005 EHR cost savings estimates.18,19

Another systematic assessment of the effects of CPOE on prescribing errors in inpatient settings was provided in a systematic review by Reckmann et al. (2009) of studies published from 1998 through October 2007.29 Overall, 9 of the 12 studies identified significant reductions, ranging from 29%-96%, in prescribing error rates with CPOE. However, 7 studies employed weak pre-versus-post designs and none was randomized. The authors noted that the base of evidence “reporting the effectiveness of CPOE to reduce prescribing errors is not compelling and is limited by modest study sample sizes and designs,” concluding that a “stark comparison might be drawn between the quality of evidence on e-prescribing systems and the investment that is made in ensuring that drugs and other medical devices are safe and effective before wide-spread use.”29

**Effects of CPOE in Outpatient Settings**

In the systematic review of CPOE with decision support in outpatient settings, Eslami et al. identified 12 studies, including 4 RCTs, of cost/efficiency.24,25 Positive outcomes were documented in 5 of the 12 studies overall. However, no randomized studies found a positive effect of CPOE with decision support on cost/efficiency; 3 of the 4 RCTs found no statistically significant effect, and 1
reported that the effect of decision-supported CPOE on cost/efficiency was negative (i.e., higher cost with decision support). That study, reported by Tierney et al. (2005), examined the effect of providing care suggestions based on “published evidence-based guidelines” for the treatment of asthma and COPD to providers based on patient-specific data as a supplement to an existing CPOE system. The finding of higher costs with decision support was inconclusive because of “a small number of extremely high-cost hospitalizations” in 1 cohort.30

Eslami et al. identified only 4 studies of medication safety in outpatient CPOE, of which only 1 was randomized.35 All 4 assessed CPOE combined with clinical decision support: (a) The sole RCT, reported by Rotman et al. (1996), identified no significant effect for CPOE on the rate of clinically significant drug interactions, comparing decision-supported CPOE with paper prescriptions; however, the trial has no applicability today because it was conducted in 1994-1995 and because the intervention group used CPOE for only 2.8% of prescriptions.31 (b) A pre-post assessment without a comparison group, conducted by Steele et al. (2005), found that implementation of an alerting system for drug-laboratory problems (i.e., notification of a missing test or an abnormal test value) was associated with statistically significant increases in ordering of the necessary laboratory test (from 38.5% to 51.1%, P < 0.001) and stoppage of the medication ordering process (from 5.6% to 10.9%, P = 0.03) but no significant change in definite or probable ADEs defined by Naranjo scoring (from 10.3% to 4.3%, P = 0.23).32 (c) An observational analysis by Weingart et al. (2003) found that physicians overrode approximately 90% of drug allergy and high-severity drug interaction alerts, with no significant difference in ADE rates for overrides versus accepted alert cases.33 (d) A prospective cohort study by Gandhi et al. (2003) found no significant differences in either prescribing errors or ADEs comparing computerized with handwritten prescribing.34 However, the CPOE sites in the Gandhi et al. study used “basic” computerization only, without checks for allergies and drug interactions.35 A later, more detailed examination of the 2003 Gandhi et al. study data, conducted by physician reviewers, indicated that CPOE with advanced decision support (e.g., drug-dose checking and drug-frequency checking) could have prevented an estimated 138 of 143 prescribing errors (97%) and 59 of 62 potential ADEs (95%).35

A current (October 2010) PubMed search on the terms “CPOE” and “computerized prescription order entry” with “safety” limited to RCTs produces only 3 studies, all conducted in the same large health maintenance organization (HMO) in 2006 and 2007.36-38 When all HMO members aged 65 years or older were randomized to a CPOE-based alerting system that triggered when any of 11 potentially inappropriate medications for the elderly were prescribed (n = 29,840) or to a “usual care” control group (n = 29,840), Raebel et al. found that the rate of potentially inappropriate dispensings per 100 patients during the 1-year follow-up was 1.85, compared with 2.20 in the control group (difference of 0.0035 dispensings per patient, P = 0.002).36 However, in a similarly designed study targeted to pregnant women, the intervention was successful in reducing the use of pregnancy-risk medications but had to be discontinued because of false-positive alerts attributable to computer system limitations.37 Additionally, an RCT of CPOE-delivered reminders found no significant effect on provider adherence to recommended laboratory testing guidelines at initiation of pharmacotherapy.38

Commenting on the unfavorable results of their study of the effect of decision-supported CPOE on outcomes for patients with asthma/COPD in primary care, Tierney et al. reported that they “had hoped to show that computer-generated care suggestions would enhance adherence to evidence-based guidelines and have salutary effects on patient-centered and clinical outcomes. Unfortunately, none of this occurred, which surprised us …”30 Noting that previous studies had shown more positive outcomes for interventions in which physicians were given suggestions to increase preventive care or use of cost-effective treatments, Tierney et al. concluded that despite the IOM’s strong support for EHR use as a care improvement mechanism, “expensive and sometimes intrusive innovations need to be thoroughly tested in rigorous trials before broad implementation.”30

Evidence of “e-Iatrogenesis” in Published Research

The report by Strom et al. was not the first to identify patient care problems attributable to use of HIT.2,30-41 In 2004, Ash et al. reported the results of exploratory observational research including formal interviews with medical staff to assess the effects of patient care information systems (PCIS) on workflow and accuracy in hospitals located in Australia, the Netherlands, and the United States.2 Although acknowledging the “promise” of PCIS to facilitate appropriate care, the researchers reported “unintended consequences” attributable to “a mismatch between the functioning of the PCIS and the real-life demands of health care work.” Problems identified by Ash et al. included (a) juxtaposition error, in which the wrong medication was ordered because “something is close to something else on the screen and the wrong option is too easily clicked in error;” (b) new patient safety risks because of staff “workarounds” introduced in response to system inflexibility; and (c) “loss of overview” in which “the user had to switch among multiple windows” to obtain information about a patient.

For example, one U.S. clinician interviewed by Ash et al. reported that: “You would order [medication] on one patient and it would, [because] of the vagaries of the light pen system, you thought you were ordering it on one, and it was really ordered on somebody else and somebody got the wrong medication and that sort of thing.”2 Similarly, a U.S. pharmacist described an instance in which a drug that had been...
ordered 3 times daily had been discontinued after a dose of the medication had already been administered, but the system would not permit the nurse to record the dose “because the system considered it an incomplete execution of the task.” Providers also reported information overload because of an excessive volume of alerts and problems arising because of the tendency of users to “cut and paste” information from one patient record to another.

Noting that their evidence was qualitative, not quantitative, Ash et al. called in 2004 for additional research into “subtle silent errors” in which “the intended strengthening of one link in the chain of care actually leads unwittingly to a deletion or weakening of others.” Subsequent work published by the same research team in 2006 and 2007 first used observation and semi-structured interviews at 5 U.S. hospitals to identify a framework for classifying major categories of unintended consequences attributable to “computerized provider order entry” (encompassing CPOE and other electronic orders), then produced quantitative information about the rates of occurrence of each consequence type based on telephone interview data obtained from representatives of 176 U.S. hospitals (response rate = 47%).

Based on the earlier qualitative work, the 8 major categories identified by the research team for inclusion in the hospital survey were (a) additional workload for physicians to “enter required information, respond to alerts, deal with multiple passwords, and expend extra time;” (b) workflow problems because of mismatches between system requirements and work routine; (c) ongoing “demands” for more and improved hardware and software; (d) “illusion of communication” problems because “people think that just because the information went into the computer the right person will see it and act on it appropriately;” (e) negative staff emotions; (f) new errors that threaten patient safety, such as juxtaposition errors and information overload; (g) a shift in power (i.e., removing some autonomy from physicians); and (h) “overdependence on technology,” leading to lost productivity in the event of system failure. Categories rated by 80% or more of respondents as “moderately to very important” (defined by the research team as a response of “yes” to indicate that the problem existed plus a rating of 3, 4, or 5 on a Likert-type scale of 1 “not at all important” to 5 “very important”) included workflow problems, communication problems, overdependence on technology, system demands, and negative emotions. Increased workload, new kinds of errors, and power shift were rated as moderately to very important by 72%, 47%, and 36% of respondents, respectively.

Two aspects of the 2007 survey by Ash et al. are notable. First, questions were framed in a way that suggested to respondents that the problems existed before asking whether they were an issue for the respondent’s institution. For example, the question about emotion asked: “We have seen many emotional responses to the system. Have you seen users express strong feelings about CPOE?” Similarly, the question about system demands asked: “The information system typically needs a great deal of support in terms of maintenance, training, updating order sets, etc. Has this been an issue in your organization?” Thus, it is possible that respondents were biased by the question wording to report difficulties in using HIT. However, the text of the respondent comments included in the report by Ash et al. suggests that the preponderance of the views expressed by respondents were based on personal experience and not interview bias, for example:

- “The need for constantly upgrading old computer equipment is a huge issue.”
- “[W]e weren’t aware that so much support resources would be needed; we way under forecasted.”
- “Someone asked me, how does it feel to be the most hated person in this institution?”
- “A doc threw a computer at me! The screaming is slowly improving after 3-4 years of meetings.”

Second, the results of the 2007 survey by Ash et al. do not appear to be attributable to inexperience in using HIT. The median time since system implementation among study hospitals was 5 years (range 6 months to 25 years); and a median of 91% of provider orders were electronic. Additionally, Spearman’s rho correlations showed no statistically significant relationships between responses to any of the 8 items and time since CPOE implementation.

Like Ash et al., Koppel et al. (2005) used a combined qualitative-quantitative method to assess medication errors attributable to a widely used CPOE system in a tertiary-care teaching hospital from 2002 to 2004, approximately 5 to 7 years after CPOE implementation. Using a variety of data-gathering techniques including structured interviews, real-time observation, focus groups, and written questionnaires completed by house staff, Koppel et al. identified 22 “previously unexplored medication-error sources that users report to be facilitated by CPOE.” The authors grouped these into 2 major categories, (a) information fragmentation and failure of systems integration and (b) human-machine interface problems.

Information fragmentation and systems integration failures that survey respondents reported as occurring at least once in the previous 3 months included use of CPOE displays by 73% of respondents to identify minimally effective or usual dosages, whereas the display actually portrayed dosages that “are based on the pharmacy’s warehousing and purchasing decisions, not clinical guidelines,” that is, the strength of the tablet stocked on the pharmacy’s warehousing and purchasing decisions, not clinical guidelines, that is, the strength of the tablet stocked by the hospital pharmacy. Koppel et al. also identified delays in cancelling medications because of an interface that required using multiple screens to change a single patient’s medications (reported by 51% of respondents) and gaps in antibiotic therapy because of the absence of reminders that the system required...
reapproval of antibiotics every 3 days (83% of respondents). Human-machine interface flaws identified by Koppel et al. included difficulties in identifying a patient from the CPOE display (55%), uncertainty about the current medication list because it appeared on up to 20 screens (71%), delays in ordering medications because of system shutdowns (84%), and system inflexibility in “specifying medications or ordering off-formulary medications” (92%). The percentages of respondents reporting that problems occurred “about a few times a week” or more often during the past 3 months were lower, but still troubling—for example, 40% for gaps in antibiotic therapy, 55% for difficulties in ordering medications because of system inflexibility, and 46% for uncertainty about patients’ medications because of display problems. An editorial in JMCP more than 5 years ago highlighted the important work of Koppel et al. regarding the potential for CPOE to introduce harm and urged the application of the principles of continuous quality improvement (CQI) prior to widespread adoption of CPOE and clinical decision support systems.

In their 2009 systematic review of inpatient prescribing, Reckmann et al. found that despite generally favorable results for CPOE, several errors were more likely with CPOE than with paper-based prescribing. These included duplicate prescription orders because of “fragmented” screen design (i.e., the inability to view all medications simultaneously), selection of inappropriate or erroneous products or dosages from drop-down menus, and missed drug allergies. In commenting on the work of Ash et al., Weiner et al. (2007) coined the term “e-iatrogenesis” to describe “patient harm caused at least in part by the application of [HIT].” Noting the increasing importance of examining unintended consequences “as CPOE and other components of [HIT] logistically diffuse across the U.S. health care system,” Weiner et al. described their work with a small consortium of HIT adopters to develop and improve HIT: “Universally, we are hearing reports that e-iatrogenesis, and the broader area of unintended consequences, is [sic] of concern at all of these top-notch organizations. What will happen as HIT is rolled out at organizations further down the diffusion curve?”

**Limited But Growing Evidence of Challenges in “Real-World” Use of HIT**

A very partial answer to the question posed by Weiner et al. about unintended consequences associated with use of HIT in routine practice was provided in testimony by Jeffrey Shuren, Director of the U.S. Food and Drug Administration (FDA) Center for Devices and Radiological Health, to the Adoption/Certification Workgroup of the HIT Policy Committee of the DHHS on February 25, 2010. That Shuren’s testimony raised concerns about HIT was ironic because the committee before which he testified had been created as part of the HITECH act to promote EHR use. Although emphasizing that “the FDA seeks to support the benefits that HIT can bring through improvements in individual patient care and the overall health-care system,” Shuren highlighted what he described as “serious safety concerns” attributable to HIT malfunctions and human interface problems.

Shuren testified that according to the provisions of the Federal Food, Drug, and Cosmetic Act, “HIT software is a medical device.” Although the FDA has “largely refrained from enforcing our regulatory requirements with respect to HIT devices,” limited data on patient safety are available because some HIT vendors and users voluntarily report HIT-related adverse events to the FDA using the Medical Device Reports (MDR) system that is typically required of device manufacturers. Analysis of these data by the FDA for the previous 2 years identified “260 reports of HIT-related malfunctions with the potential for patient harm—including 44 reported injuries and 6 reported deaths.” Examples cited by Shuren included the placement of a nuclear medicine study in the wrong patient’s electronic file because of a software error; an “improper database configuration” that “caused manual patient allergy data entries to be overwritten during automatic updates of patient data from the hospital information system;” failure to display patient allergy information properly because of “a missing codeset;” and a vendor interface problem that caused computerized tomography images to “flip” (i.e., display in mirror image). Because the data were reported voluntarily, Shuren added that the incidents “may represent only the tip of the iceberg in terms of the HIT-related problems that exist.”

Less than 2 weeks after Shuren’s testimony, the Veterans Health Administration (VA) issued a patient safety alert indicating that access to all electronic Department of Defense (DoD) records had been disabled on March 1, 2010, because of the “potential for incorrect or incomplete display of [DoD] records” when using the VA’s EHR system. The problem had been discovered when a clinician had accessed the EHR of a female patient and noticed that it contained a prescription for vardenafil, which actually had been ordered for a different (male) patient. Investigation revealed that EHR queries “may display no data, a subset of data, incorrect data, or the complete data. The VA clinician may see the patient’s data during one session, but another session may not display the data previously seen. This problem occurs intermittently and has been reported when querying DoD Laboratory, Pharmacy, and Radiology Reports.” Anecdotal reports of system shutdowns and user interface problems in other EHR systems are emerging among policy blog writers but at this writing have not been explored extensively in the popular press or peer-reviewed literature.

**CQI for CPOE**

A potentially important but seldom discussed benefit of CPOE is the provision of information not just during the act of
prescribing, but also in databases generated from the electronic prescriptions themselves. These databases permit ongoing nationwide monitoring and quality improvement “in a way that is simply not possible with paper… [representing] what amounts to a national air traffic control system for prescriptions,” according to an industry quality officer.46 The CPOE industry is moving toward a system in which information gathered from these databases can enable timely identification and correction of specific quality problems.

For example, monitoring studies using CPOE databases have pointed to discrepancies between the contents of “free text” and “structured” (e.g., pre-specified drop-down menu) fields in electronic prescriptions as a source of potential new safety problems.59,30 In a retrospective review of more than 400,000 electronic prescriptions in a large outpatient health care system, Palchuk et al. (2010) found that 42.9% contained a free-text instruction. Of 2,914 prescriptions with free-text instructions that were sampled, 470 (16.1%) contained at least 1 discrepancy and 79 (2.7%) contained more than 1 discrepancy. Assessment by pharmacist reviewers indicated that 394 (83.8%) of the 470 discrepant prescriptions could lead to an ADE; these included under- or overdosing of up to 55-fold, wrong route (e.g., intravenous vs. intravaginal), and dose escalation or tapering problems. Reviewers judged that 79 of the 470 discrepancies (16.8%) had “the potential for an ADE severe enough to lead to a hospital admission and/or death.”50

Data of this type have permitted industry monitors to begin honing in on configurations that can foster quality problems.38 The e-prescription network SureScripts issued guidelines for creating high-quality electronic prescriptions in ambulatory settings in 2010 and plans a future publication “that will address issues such as root-cause analyses of e-prescriptions that do not meet these guidelines, as well as outline preventative and corrective measures to mitigate any problems that such analyses identify.”51 Noting that “experience has shown that a number of prescribing data fields are particularly susceptible to improper use,” the guidelines remind prescribers of the importance of consistency across fields, standard naming conventions, watching for truncation of fields when entering free text, and use of appropriate numeric measures. The latter category is particularly notable because of the potential for dosing errors; for example, the guidelines point out that trailing zeros (e.g., X.0 instead of 0.X in specifying tablet strength) can lead to 10-fold overdoses, and use of the abbreviation “ug” instead of “mcg” can lead to misinterpreting the intended “microgram” as “milligram.”51

Proposals to Monitor HIT Device Safety: Going Forward or Going Nowhere?

To balance the benefits of HIT with “minimizing the risks that this technology can potentially create,” Jeffrey Shuren presented in his February 2010 testimony 3 regulatory options ranging from less to more intensive: (a) required registration of HIT devices and submission of MDRs to the FDA to enable postmarketing surveillance if needed; (b) required registration and submission of MDRs plus adherence to the FDA’s Quality Systems Regulation (QSR) process for “minimum guidelines to assure the quality and consistency of products on the market” (e.g., procedures for handling complaints and for correcting problems); or (c) application of the FDA’s “traditional regulatory framework, in which HIT device manufacturers would be required to meet all the same regulatory requirements as other, more traditional devices, including risk-based premarket review” of “the safety and effectiveness of high- and medium-risk HIT devices before they go into market use.” The third option might also include FDA approval of installation plans, hazard analysis, product label, or postmarket studies.45

On April 21, 2010, the DHHS HIT Policy Committee made recommendations to David Blumenthal, the DHHS National Coordinator for Health Information Technology, to address the “vitally important topic” of “patient safety related to the use of [EHRs].”52,53 Foremost among these were the adoption of a “national, transparent oversight process and information system” including “standardized data reporting formats that facilitate analysis and evaluation” and “a formal study to thoroughly evaluate HIT patient safety concerns, and to recommend additional actions and strategies to address those concerns.”52 These suggestions are consistent with the spirit of the ongoing CQI efforts within the CPOE industry.46 However, a safety monitoring system established according to the committee’s suggestions would likely require additional features in EHR and CPOE devices, as well as broader criteria and cultural changes for reportable events. For example, recommendations included certification criteria for EHRs incorporating “functionality that makes it easier for clinician-users to immediately report any problems/concerns with information that appears on screens (a ‘feedback button’);” the “[capacity] to monitor not only actual adverse events but also “near-miss patient harms;” and “whistle-blower” protection for those reporting HIT-related adverse events.52

At the same time, however, the committee expressed concerns about the “potential for increased [FDA] regulation of HIT systems.”52 These concerns included the recognition that HIT-related problems can occur even in a properly functioning device (i.e., human interface issues that might fall outside FDA’s jurisdiction); the possibility that the costs of compliance with FDA regulation could be “a barrier to entry for small vendors;” and inconsistency between the FDA’s QSR process and “the incremental nature of HIT development. … By hampering and slowing the ability of vendors to continuously improve systems, thus making them safer, such a process could actually work against the safety efforts we are proposing.” The committee instead suggested collaboration between DHHS and the FDA on safety matters, including EHR certification criteria.
The committee also noted its position “that the biggest risk to patient safety would be to either avoid or delay the proper implementation of EHR and CPOE systems.”

On April 29, 2010, in an apparent early response to the committee’s recommendations, Blumenthal told attendees at a national conference on HIT that a “preliminary investigation” into the concerns raised by the FDA’s Jeffrey Shuren in February 2010 had shown that the evidence was “anecdotal and fragmented.” The logical flaw in using the anecdotal nature of voluntarily reported safety evidence as a reason to reject a mandatory reporting process is obvious. Nonetheless, at this writing, no decision about the HIT committee’s recommendations to protect patient safety has been announced.

Hubris, Humility, and Hippocrates

In health care policy making, as in any activity, it is tempting to assume that all our good ideas will yield the desired outcome—but often, they don’t. It is also tempting to assume that it is acceptable to put well-intentioned interventions into practice without first subjecting them to rigorous testing—but often, this strategy results in unintended and undesirable consequences.

The truth is that we don’t know everything about the effects of HIT (or any health care intervention), much as we would like to. More RCTs—the best way to distinguish supposition from sound policy decision making—are needed to assess the incidence and types of errors for various HIT configurations and decision support features as rapid adoption of these potentially practice-changing technologies moves forward. The limited evidence currently available suggests that a key issue may be the tradeoff between strength and flexibility—that is, how to design a system that harnesses the power of data in providing actionable safety-enhancing information to clinicians (e.g., treatment guidelines or drug interaction warnings) while permitting overrides of inappropriate care suggestions or allowing for instructions in free-text fields to handle nonstandard patient care situations. Additionally, like any good tool, HIT requires ongoing monitoring for gaps between ideal use and real-world use. In expansion of HIT to include decision support, especially “nearly hard stop” features such as that studied by Strom et al., perhaps a key guiding principle should be primum non nocere (first, do no harm).

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Lessons learned from randomized trials and recent experience with health information technology: Promising interventions meet real-world patient care.


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