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- Subject Reviews
- Formulary Management
- Contemporary Subjects
- Brief Communications
- Editorials/Commentary
- Letters

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• abstract: no more than 650 words
• keywords: follows the abstract

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Tables and figures (generally no more than a total of 6). Submit referenced tables and figures on separate pages with titles and captions, as necessary, at the end of the manuscript; match symbols in tables and figures to explanatory notes, if included. May use 10-point font.

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• certifies that the paper has not been accepted for publication or published previously and that it is not under consideration by any other publication, and
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Reference

ike contestants in a beauty pageant, the 12 vessels in Dante Marioni’s Colored Vessel Display blown-glass installation have taken their place onstage and wait in eager anticipation for the judges’ decision. But no panel of judges would be able to choose a winner in this contest. Though diverse, they are all equal in beauty. Marioni selected a variety of festive colors for his installation, and adorned each receptacle with whimsical contrasting trim. Some of the accents are more symmetrical than others, yet every vessel achieves a delicate visual balance.

Marioni was born and reared in Mill Valley in the San Francisco Bay Area. He comes from an artistic family—his father, Paul Marioni, is a glass master, one of his uncles is a painter, and another, a Bay Area conceptual artist. “I wouldn’t have gotten into glass if it weren’t for my father,” he readily admits. Marioni first started blowing glass at the tender age of nine, when he accompanied his father on visits to Jay Musler’s studio in Greenbrae, California.

Marioni’s father began his career by making stained-glass windows, and he continues to make a name for himself creating glass sculptures, painted glass pieces, and cast windows. In 1979, he accepted a commission in Seattle for a large architectural glass installation. In 1981, at the age of 16, Marioni was hired as an apprentice at the Glass Eye, a glass-blowing studio and showroom in Pike Place Market. He was willing to do everything from stoking the furnace to sweeping up broken glass. After graduating from Garfield High School, Marioni went to work full time at the studio. It was there that he encountered the first of several important mentors. Benjamin Moore, a Venice-trained glassblower, was working at the Glass Eye, and Marioni watched in wonder at “the first person I’d seen who could blow symmetrydly articulate forms.” This was a turning point for Marioni. Until then, he was unsure about pursuing a vocation in blown glass, but now he was firmly committed to the field.

After a year at the Glass Eye, Marioni enrolled in a two-month-long glass-blowing class at the Penland School of Crafts in the Blue Ridge Mountains of western North Carolina. His instructor was another Italian-trained master, Fritz Dreisbach. Marioni observed Dreisbach as he reinterpreted traditional Venetian glass-blowing techniques, and it inspired him to create his first significant body of work: tall tumblers in green, blue, orange, and purple. Not unlike some business owners who frame the first dollar they ever made, Marioni keeps the tumblers on a shelf in his studio.

Returning to the Glass Eye, he began making the wine glasses that are now a staple in his repertoire. It was at this time that Marioni met Lino Tagliapietra, who was teaching at the Pilchuck Glass School in nearby Stanwood, Washington. (Tagliapietra was JMCP’s April 2006 cover artist.) “Lino’s probably the best-known glass maestro alive today,” says Marioni. “He’s the person who’s had the greatest influence on my work.”

By 1984, Marioni and his father had founded the blown-glass studio where they both work today. He says that glass blowing is a team effort, usually involving two or three people, but for larger pieces, as many as a dozen people may be required. Marioni has worked with his assistant, Janusz Pozniak, for the last 16 years. “Janusz and I have very different artistic styles, but I think we complement one another,” he says.

Marioni derives his inspiration from several different sources, including ancient Greek and Etruscan pottery and Venetian glass work from the 1930s and ‘40s. He is a true craftsman as well as an artist, making each new shape over and over, without color, until it reaches the form he desires. Only then does he begin to add the vibrant colors that have become his trademark. In the process, Marioni’s vases are transformed from blown-glass objects into objets d’art. His superbly crafted vessels have been described as “crossing the line into the realm of sculpture.”

To see numerous examples of this gifted artist’s creations, visit his Web site: www.dantemarioni.com. A book about Marioni, Dante Marioni: Blown Glass, contains many stunning photographs of his artwork.

Regarding his career, Marioni declares, “I’ve always been lucky. I have complete artistic freedom—I get to go into my studio and create whatever I want.” Although he has done some commissioned work, most of the pieces that he produces are sold through galleries and other exhibitions. Marioni will be having a significant exhibit at PISMO Gallery in Aspen, Colorado, in July. His work can be found in many other major galleries throughout the U.S., including PISMO Fine Art Glass in Denver; William Traver Gallery in Seattle; Marx-Sauders Gallery in Chicago; Hawk Galleries in Columbus, Ohio; Maureen Littleton Gallery in Washington, D.C.; and Holsten Gallery in Stockbridge, Massachusetts.

Marioni’s glass art is also in numerous public and private collections in this country and throughout the world.

Sheila Macho
Cover Editor

COVER CREDIT

SOURCE
Interview with the artist.
Effects of a Step-Therapy Program for Angiotensin Receptor Blockers on Antihypertensive Medication Utilization Patterns and Cost of Drug Therapy

Krista Yokoyama, PharmD; Winnie Yang, PharmD, BCPS; Ronald Preblick, PharmD, MPH; and Feride Frech-Tamas, MPH, RPh

ABSTRACT

BACKGROUND: Step therapy for angiotensin receptor blockers (ARBs) requiring prior use of angiotensin-converting enzyme inhibitors (ACEIs) is a common cost-containment intervention in managed care.

OBJECTIVE: This study was designed to assess the effectiveness of the step-therapy intervention for ARBs, including ARB/hydrochlorothiazide (HCTZ) combinations, as measured by prescription use patterns and antihypertensive drug ingredient costs.

METHODS: Rejected and paid pharmacy claims data were evaluated from 3 health plans with a total membership of approximately 1 million. These plans had implemented a step-therapy intervention for ARBs from May 1, 2001, through February 28, 2003. Patients in the intervention group who had experienced a claim rejection for an ARB within the first 6 months of program implementation (i.e., had had no ACEI [or ACEI/HCTZ combination] or ARB [or ARB/HCTZ] claim in the preceding 3 months) were followed for 1 year after the ARB claim rejection. The rate of initiation of ARB versus ACEI and other outcomes was compared with similar data from a health plan with approximately 2 million members that did not have a step-therapy intervention for ARBs (comparison group). Mean and median total antihypertensive drug ingredient costs per patient and per day of therapy over 12 months were analyzed for the intervention and comparison groups. One pharmacy benefit manager administered the pharmacy benefits for the intervention and comparison health plans during the entire study period from May 1, 2001, through February 28, 2004, and the drug formulary was similar for all health plans.

RESULTS: In the step-therapy health plans, before the criterion for 15 months of continuous eligibility was applied, there were 8,904 patients (approximately 0.9% of health plan members) who either attempted and were rejected for an ARB or who newly started ACEI therapy, compared with 44,788 patients (approximately 2.2% of members in the comparison health plan) who newly started ARB or ACEI therapy without the step-therapy intervention. After the eligibility criterion was applied, there were 6,758 intervention health plan members (0.7% of members) and 33,709 comparison health plan members (1.7% of members) in the 2 study groups. In addition to the smaller proportion of total members affected by the intervention in the ARB step-therapy health plans, a smaller proportion of ARB/ACEI patients attempted to obtain an ARB (1,296/6,758 or 19.2%) compared with the health plan without step therapy (8,697/33,709 or 25.8%, P < 0.001). Of the 1,296 patients who attempted to obtain an ARB and were rejected in the step-therapy group, 578 patients (44.6%) went through the prior-authorization process and received an ARB as initial therapy, 632 patients (48.8%) received other antihypertensive therapy, and 86 patients (6.6%) did not receive any antihypertensive therapy within the 12-month follow-up period. In the 12 months of follow-up, 51.1% (323/632) of patients in the intervention group who received other antihypertensives as index therapy switched to or added an ARB, and 1,234 of total ACE/ARB patients (n = 6,758, 18.3%) received ARB therapy in the health plan with step therapy compared with 10,498 of 33,709 total ACE/ARB patients (31.1%) who received ARB therapy in the health plan without step therapy. The mean antihypertensive drug cost per patient was lower in the intervention group ($370.00) than in the comparison group ($445.12; P < 0.001), and the average cost per day of antihypertensive drug therapy was 12.8% lower in the step-therapy group ($0.82) than in the comparison group ($0.94). Unadjusted annual cost savings were $75.12 per patient, and ordinary least squares regression analysis showed that the ARB step-therapy intervention was associated with $43.91 in antihypertensive drug cost savings per patient over 12 months.

CONCLUSIONS: Within 12 months of follow-up, a step-therapy intervention for ARBs was associated with an 18% ratio of ARB users to total ACEI/ARB users compared with a 31% ratio in a comparison health plan without the ARB step-therapy intervention. Approximately 45% of patients who did not receive an ARB as a result of the step-therapy intervention had either switched to or added an ARB within 12 months of the intervention, and almost 7% of patients did not receive any antihypertensive therapy. Antihypertensive drug cost was about 13% lower for the ACEI/ARB patients in the intervention group, creating approximately $368,000 in savings in 1 year or $0.03 per member per month across the 1 million health plan members.

KEYWORDS: Angiotensin receptor blockers, Step therapy, Prior authorization, Pharmacy costs

J Manag Care Pharm. 2007;13(3):235-44

Note: An editorial on the subject of this article appears on pages 284-86 of this issue

The clinical benefits of angiotensin receptor blockers (ARBs) and angiotensin-converting enzyme inhibitors (ACEIs) in the treatment of hypertension have been well established.1-3 Because of the clinical efficacy and safety of these drugs, ARBs and ACEIs are recommended in the Seventh Report of the Joint National Committee on Prevention, Detection,
A step-therapy intervention can be implemented using an automated concurrent claim review process in which the pharmacy benefits manager (PBM) searches its drug claims history for evidence of prior use of the required step-therapy drug. Alternatively, a step-therapy intervention can involve a manual process with review of the patient's drug use history after the claim rejection. In the case of automated concurrent claim review ("smart edit") for an ARB step-therapy intervention, an ARB claim (including an ARB in combination with hydrochlorothiazide [HCTZ]) would be approved only with previous history of use of an ACEI (including an ACEI in combination with HCTZ) or if the patient had previously received an ARB. In most cases, when the patient is unable to get the ARB medication, the pharmacist will contact the prescriber to obtain a verbal order for an alternative medication.

Prior experience with step therapy in other disease states suggests that more than 50% of patients prescribed cyclooxygenase-2 (COX-2) inhibitor therapy did not attempt a PA following a point-of-care pharmacy claim rejection. Another study found that up to 70% of patients did not attempt to obtain a PA after their pharmacy claim for a COX-2 was denied. Several studies have been conducted to determine the effect of PA on health outcomes, focusing on direct costs and health care resource use among those affected by a PA. However, little is known about the antihypertensive drug use patterns of members when a step-therapy program is in place for ARBs.

This study was designed to evaluate the hypertension-related pharmacy use and costs for 3 managed care plans that implemented an ARB step-therapy intervention compared with 1 health plan with no ARB step-therapy intervention. The step-therapy intervention employed a "smart edit" in which each new claim for an ARB triggered an electronic search of the patient's pharmacy claim history for evidence of prior use of an ACEI, including an ACEI in combination with HCTZ, or an ARB, including an ARB/HCTZ, in the preceding 3-month period. The ARB claim was rejected if there was no prior use of these drugs and the pharmacist or patient had to contact the prescriber to obtain either an alternative to the ARB or a PA (e.g., the patient had attempted an ACEI claim previously that was not in the pharmacy claims history).

### Table 1: Description of Health Plans With and Without ARB Step Therapy

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Region</th>
<th>Approximate Membership</th>
<th>Step-Therapy Program Implementation Date</th>
<th>Period of Service Dates for Patient Identification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step therapy</td>
<td>Northeast</td>
<td>500,000</td>
<td>August 13, 2002</td>
<td>September 1, 2002-February 28, 2003</td>
</tr>
<tr>
<td>Step therapy</td>
<td>Midwest</td>
<td>150,000</td>
<td>January 1, 2002</td>
<td>January 1, 2002-June 30, 2002</td>
</tr>
<tr>
<td>Step therapy</td>
<td>Midwest</td>
<td>350,000</td>
<td>April 8, 2001</td>
<td>May 1, 2001-October 31, 2001</td>
</tr>
<tr>
<td>No step therapy</td>
<td>West</td>
<td>2,000,000</td>
<td>N/A</td>
<td>September 1, 2002-February 28, 2003</td>
</tr>
</tbody>
</table>

* N/A = not applicable.

### Table 2: Average Actual Copayments for ARBs and ACEis

<table>
<thead>
<tr>
<th>Drug Type</th>
<th>Step-Therapy Group ($)</th>
<th>Comparison Group ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generic ACEI</td>
<td>7.43</td>
<td>8.78</td>
</tr>
<tr>
<td>Formulary brand ACEI</td>
<td>13.18</td>
<td>17.70</td>
</tr>
<tr>
<td>Nonformulary brand ACEI</td>
<td>30.94</td>
<td>25.37</td>
</tr>
<tr>
<td>Formulary brand ARB</td>
<td>16.15</td>
<td>18.19</td>
</tr>
<tr>
<td>Nonformulary Brand ARB</td>
<td>30.69</td>
<td>28.73</td>
</tr>
</tbody>
</table>


† The drug formulary contained (a) 7 generic ACEIs and ACEI/HCTZs (captopril, enalapril, fosinopril, lisinopril, captopril/HCTZ, enalapril/HCTZ, and lisinopril/HCTZ) with a tier-1 copayment and (b) 7 of 21 available brand ACEI and ACEI/HCTZ combinations and 6 of 12 available brand ARB and ARB/HCTZ combinations with a tier-2 copayment.

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; HCTZ = hydrochlorothiazide.

Evaluation, and Treatment of High Blood Pressure (JNC 7) guidelines. However, with the availability of generic ACEIs and the relatively higher cost of the ARBs, some managed care plans have implemented cost-containment strategies, including preference for ACEI therapy to ARBs.

Managed care organizations are increasing adopting interventions such as step-therapy requirements and prior-authorization (PA) programs to contain costs while attempting to improve patient care. Step-therapy criteria are widely adopted by managed care plans to guide appropriate medication use and manage the cost of more expensive therapy. In 2005, nearly 80% of commercial plans and 64% of Medicare Advantage plans reported using step-care protocols or treatment guidelines. Additionally, in 2005, 96% of commercial plans and 73% of Medicare Advantage health plans reported managing the prescribing of drugs outside of formularies via PA. A survey conducted in 2004 of 404 employers representing 8.6 million members found that the use of step-therapy edits increased from 22% of employers in 2000 to 28% in 2002 and 45% in 2004.
Methods

Study Design and Data Source

A retrospective cohort study was designed to assess the impact of an ARB step-therapy intervention on the use of antihypertensive agents during a 12-month follow-up period. The intervention group included members from 3 health plans in which pharmacy benefits were managed by a PBM and where an ARB step-therapy program was in place between May 1, 2001, and February 28, 2003 (Table 1). The 3 health plans were commercial managed care plans located in the Northeast and Midwest. Membership in the 3 plans ranged from 150,000 to 500,000 patients.

A comparison group of members was selected from 1 commercial managed care health plan in the West without ARB step therapy in 2002 or 2003 and with average membership of 2 million. All health plans had a mix of 2-tier and 3-tier pharmacy benefit plan designs with similar average copayments for 3-tier business (Table 2). The drug formulary included 7 generic ACEIs and ACEI/HCTZ products (captopril, enalapril, fosinopril, lisinopril, captopril/HCTZ, enalapril/HCTZ, and lisinopril/HCTZ). Seven of 21 available brand ACEI and ACEI/ HCTZ products and 6 of 12 brand ARB and ARB/HCTZ products were on the drug formulary. Mail order was available in all health plans, and members were allowed to fill prescriptions for up to a 3-month (90-day) supply. In general, the ratio of mail order to community pharmacy was no more than 5% to 6% of total prescriptions dispensed.

All rejected and paid pharmacy claims data for ARBs, ARB/ HCTZ combinations, ACEIs, and ACEI/HCTZ combinations were extracted using the Generic Product Identifier code (Medi-Span classification system). For simplification, future references to ARBs or ACEIs in this article include ARB/HCTZ combinations and ACEI/HCTZ combinations.

Patients in the intervention group who had encountered a claim reject for an ARB or had had a paid claim for an ACEI over the 6-month identification period and had no ARB or ACEI claim in the previous 3 months (new starts) were followed for 1 year. The patient identification period in the intervention health plans was May 1, 2001, through February 28, 2003, based on the initiation of the step-therapy intervention for each plan (Table 1). Patients in the comparison health plan who were newly started on an ACEI or ARB during a 6-month selection period were identified from paid claims data with dates of service from September 1, 2002, through February 28, 2003 (Figure 2). The index date was defined as the date of the first attempt to obtain an ARB (intervention group) or the initial fill date for an ARB (comparison group) or ACEI (intervention or comparison groups). Combination treatment was defined as having claims for another antihypertensive drug on the index date or in the previous 3 months with overlapping days supply. New start patients were included in the study if they were aged ≥18 years on the index date and were continuously enrolled for the 3-month preindex and 12-month follow-up periods (Figures 1 and 2).

Outcome Measures

The outcome measures for the group with step therapy versus the comparison group without step therapy included the rate of initiation on an ACEI or ARB and the proportion of patients who attempted to receive an ARB (and had had no ARB or ACEI claim in the previous 3 months in the step-therapy group) or who were newly started on an ARB. The type of initial antihypertensive therapy received by patients in the intervention group following the ARB claim reject was also evaluated. The initial therapy in the step-therapy group was identified as the first paid claim for an antihypertensive drug following the rejected claim during the 12-month follow-up period. Additionally, the proportion of patients in the intervention group who received other
antihypertensive therapy following the rejected ARB claim, but who were switched to or added ARB therapy within 3, 6, and 12 months, was determined.

Other outcome measures for the step-therapy group versus the comparison group included antihypertensive drug use and antihypertensive drug acquisition costs. The mean and median number of claims, number of unique drugs, and days supply received were computed as well as antihypertensive ingredient cost per patient and per day of antihypertensive drug therapy over the 12-month follow-up period. Ingredient cost reported in this study is the allowed drug cost before subtraction of member cost share (copayment or coinsurance) or manufacturer rebates.

Statistics
All statistical and descriptive analyses were performed using SPSS version 14.0 for Windows (Chicago, Illinois). Mean and standard deviations were calculated for continuous variables. Chi-square test and Student’s t test were computed to test the differences between groups, and a value of $P < 0.05$ was established as a statistically significant difference. Mean, median, and 95% confidence intervals were calculated for pharmacy cost and use.

Ordinary least squares regression analysis was used to estimate the impact of the step-therapy edit on total antihypertensive drug costs during the 12-month period while controlling for potential confounding variables, such as age, gender, Chronic Disease Score (CDS), average copay per claim, and number of 30-day antihypertensive drug claims. Model diagnostics were performed, including tests for multicollinearity.

A CDS was determined for patients in the current study using the method by Clark et al. for pharmacy claims use from the 6 months before each patient’s index date to identify chronic diseases (i.e., coronary and peripheral vascular disease, hypertension, hyperlipidemia, congestive heart failure, asthma, and diabetes mellitus). Total cost weight was used as a severity measure and estimate of the patient’s total chronic disease burden.

Results
In the health plans with the step-therapy intervention for ARBs before application of the criterion for 15 months of continuous eligibility, there were 8,904 patients (approximately 0.9% of health plan members) who either attempted and were rejected for an ARB or who newly started ACEI therapy (Figure 1) compared with 44,788 patients (approximately 2.2% of members in the comparison health plan) who newly started ARB or ACEI therapy without the step-therapy intervention (Figure 2). After the criterion of 15 continuous months of eligibility was applied, 6,758 of health plan members (0.7%) were affected by the ARB step-therapy intervention versus 33,709 health plan members (1.7%) who initiated either ACEI or ARB therapy in the comparison group.

Of the 6,758 patients who met the eligibility criteria and either newly started (i.e., no ACEI or ARB in the 3-month pre-index period) an ACEI or attempted to obtain an ARB in the intervention group, the mean age (52.9 years) was lower than the comparison group (n = 33,709), which had a mean age of 57.6 years (Table 3). The gender ratio between the intervention group (54.0% male) and the comparison group (54.4% male) was similar. The mean CDS for the intervention group (1598.30) was lower than for the comparison group (1860.95).

Rate of Initiation
 Approximately 19.2% (1,296 of 6,758) of patients in the step-therapy group attempted to get an ARB compared with 25.8% (8,697 of 33,709) in the comparison group who started an ARB (Figures 1 and 2). Of the 1,296 patients who attempted to obtain an ARB under the step-therapy intervention, 44.6% received an ARB as initial therapy (via PA from the prescriber), 48.8% received other antihypertensive therapy, and 6.6% did not receive any antihypertensive therapy within 12 months of the index date (Table 4). Among the patients who attempted to get an ARB as initial therapy, a significantly greater proportion of the intervention group used antihypertensive monotherapy than did the comparison group, 50.7% versus 38.4%, respectively.
Effects of a Step-Therapy Program for Angiotensin Receptor Blockers on Antihypertensive Medication Utilization Patterns and Cost of Drug Therapy

**TABLE 3** Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Step-Therapy Group (N = 6,758)</th>
<th>Comparison Group (N = 33,709)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, mean [SD]</td>
<td>52.9 [11.2]</td>
<td>57.6 [13.4]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gender, no. male (%)</td>
<td>3,652 (54.0)</td>
<td>18,354 (54.4)</td>
<td>0.538</td>
</tr>
<tr>
<td>Chronic Disease Score, mean [SD]</td>
<td>1,598.30 [2089.83]</td>
<td>1,860.95 [2300.41]</td>
<td>0.001</td>
</tr>
<tr>
<td>No. (%) attempted ARB (step-therapy group) or started with ARB (comparison group)</td>
<td>1,296 (19.2)</td>
<td>8,697 (25.8)</td>
<td>0.001</td>
</tr>
<tr>
<td>No. (%) started with ACEI</td>
<td>5,462 (80.8)</td>
<td>25,012 (74.2)</td>
<td></td>
</tr>
</tbody>
</table>

* Mean and standard deviations were calculated for continuous variables. Chi-square test and Student's t test were computed for testing the differences between groups, and a P value <0.05 was established as a statistically significant difference.

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker.

An ARB/HCTZ diuretic combination was the most common combination therapy in the step-therapy group (n = 183, 14.1%) and in the comparison group (n = 1,590, 18.3%).

Of the 578 intervention patients who received ARB therapy following the rejected ARB claim, 233 (40.3%) received ARB monotherapy, 183 (31.7%) received an ARB/HCTZ, 145 (25.1%) received an ARB and other antihypertensive agents, 7 (1.2%) received an ARB + ACEI, and 10 (1.7%) received an ARB + ACEI + other antihypertensive (Table 4). The majority of patients (561, 97.1%) received formulary ARBs. Of the 632 intervention patients whose ARB claim was rejected and who received antihypertensive therapy other than an ARB, 104 (16.5%) received ACEI monotherapy, 320 (50.6%) received other monotherapy (119 beta-blockers, 88 calcium channel blockers [CCBs], 73 diuretics, 40 alpha-blockers), 28 (4.4%) received ACEI/HCTZ, and 208 (32.9%) received combination therapy such as an ACEI + beta-blocker or a CCB + diuretic (data not shown in Table 4).

**Pharmacy Use and Costs**

Pharmacy use, unique medications, days supply, and antihypertensive drug ingredient costs were examined in the step-therapy and comparison groups as well as in the subgroup of patients who attempted or were started on an ARB. Mean antihypertensive drug ingredient costs per patient were lower in the step-therapy group than in the comparison group despite a similar number of pharmacy claims per member, number of unique drugs per member, and days supply received (Table 6). The mean 12-month antihypertensive drug costs per patient were 16.9% lower for the step-therapy group ($370.00) than for the comparison group ($445.12, P <0.001). The mean ingredient cost per day was 12.8% lower for the step-therapy group over all for ACEI and ARB patients ($0.82) than for the comparison group ($0.94, P <0.05) and 35.9% lower than the mean cost per day ($1.28) for the 578 patients in the step-therapy group who attempted and received an ARB.

Ordinary least squares regression analysis showed that the edit was associated with a $43.91 ingredient cost savings per patient over 12 months (Table 7). Applying the $0.12 savings in direct ingredient cost per day of antihypertensive drug therapy to 3,067,351 days of drug therapy for the 6,758 patients in the step-therapy group yields 1-year drug cost savings of $368,082. For this health plan with approximately 1 million members, the drug cost savings per member per month (PMPM) associated with this ARB step-therapy intervention were at least $0.03.

**Discussion**

As pharmacy use per member continues to increase, there is a need for managed care plans to develop and implement successful cost-containment mechanisms. One of the primary goals of step-therapy programs is to promote lower-cost drugs for the majority of members and to promote cost-effective use of more expensive, newer therapies. An ARB step-therapy program was shown to reduce the number of patients receiving an ARB as initial therapy, delay the time for those patients to receive an

(P <0.001) (Table 4). An ARB/HCTZ diuretic combination was the most common combination therapy in the step-therapy group (n = 183, 14.1%) and in the comparison group (n = 1,590, 18.3%).

Of the 578 intervention patients who received ARB therapy following the rejected ARB claim, 233 (40.3%) received ARB monotherapy, 183 (31.7%) received an ARB/HCTZ, 145 (25.1%) received an ARB and other antihypertensive agents, 7 (1.2%) received an ARB + ACEI, and 10 (1.7%) received an ARB + ACEI + other antihypertensive (Table 4). The majority of patients (561, 97.1%) received formulary ARBs. Of the 632 intervention patients whose ARB claim was rejected and who received antihypertensive therapy other than an ARB, 104 (16.5%) received ACEI monotherapy, 320 (50.6%) received other monotherapy (119 beta-blockers, 88 calcium channel blockers [CCBs], 73 diuretics, 40 alpha-blockers), 28 (4.4%) received ACEI/HCTZ, and 208 (32.9%) received combination therapy such as an ACEI + beta-blocker or a CCB + diuretic (data not shown in Table 4).

**Addition of and Switch Rate to an ARB or ACEI**

Of the 632 intervention patients who attempted to obtain an ARB but received other antihypertensive therapy initially, 35.6%, 43.2%, and 51.1% were switched to or added an ARB within 3 months, 6 months, and 12 months, respectively (Table 5). Within 12 months, 25 of 104 (24.0%) intervention patients who applied for an ARB but were given ACEI monotherapy switched to or added an ARB. Of the 88 intervention patients who were given ACEI combination therapy when the ARB was denied, 33.0% (n = 29) switched to or added an ARB within 12 months. For the 5,462 intervention patients who were started initially on an ACEI, 6.1% (n = 333) switched to or added an ARB within 12 months (Table 5), similar to the 7.2% of 25,012 patients (n = 1,811) in the comparison group who started with ACEI therapy and later switched to or added an ARB within 12 months.
Effects of a Step-Therapy Program for Angiotensin Receptor Blockers on Antihypertensive Medication Utilization Patterns and Cost of Drug Therapy

### TABLE 4 Patient Characteristics and Initial Antihypertensive Therapy*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Step-Therapy Group Attempted an ARB or ARB/HCTZ (N = 1,296)</th>
<th>Comparison Group Started on an ARB or ARB/HCTZ (N = 8,697)</th>
<th>P Value‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, mean [SD]</td>
<td>53.0 [10.6]</td>
<td>58.3 [13.2]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gender, no. male (%)</td>
<td>603 (46.5)</td>
<td>4,198 (48.3)</td>
<td>0.242</td>
</tr>
<tr>
<td>Initiation of therapy, no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Started on ARB or ARB/HCTZ</td>
<td>578 (44.6)</td>
<td>8,697 (100.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Started on other anti-HTN drugs†</td>
<td>632 (48.8)</td>
<td>0 (0.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No antihypertensive drug received</td>
<td>86 (6.6)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Type of antihypertensive therapy, no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No antihypertensive drug received</td>
<td>86 (6.6)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Monotherapy</td>
<td>657 (50.7)</td>
<td>3,339 (38.4)</td>
<td></td>
</tr>
<tr>
<td>ARB only</td>
<td>233 (18.0)</td>
<td>3,339 (38.4)</td>
<td></td>
</tr>
<tr>
<td>ACEI only</td>
<td>104 (8.0)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Other monotherapy</td>
<td>320 (24.7)</td>
<td>0 (0.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Combination therapy</td>
<td>553 (42.7)</td>
<td>5,358 (61.6)</td>
<td></td>
</tr>
<tr>
<td>ARB/HCTZ</td>
<td>183 (14.1)</td>
<td>1,590 (18.3)</td>
<td></td>
</tr>
<tr>
<td>ARB + other antihypertensive</td>
<td>145 (11.2)</td>
<td>3,655 (42.0)</td>
<td></td>
</tr>
<tr>
<td>ACEI/HCTZ</td>
<td>28 (2.2)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>ACEI + other antihypertensive</td>
<td>60 (4.6)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>ARB + ACEI</td>
<td>7 (0.5)</td>
<td>15 (0.2)</td>
<td></td>
</tr>
<tr>
<td>ARB + ACEI + other antihypertensive</td>
<td>10 (0.8)</td>
<td>98 (1.1)</td>
<td></td>
</tr>
<tr>
<td>Other combination</td>
<td>120 (9.3)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
</tbody>
</table>

* Initial therapy is the first antihypertensive drug therapy the patient received following the rejected ARB (or ARB/HCTZ) claim in the 12-month follow-up period in the step-therapy group or the first therapy for the patients who newly started on ARB or ACEI in the step-therapy and comparison groups.

† The distribution (no., %) of the 632 patients who started on an antihypertensive drug other than an ARB subsequent to the ARB step-therapy claim rejection was 104 (16.5%) on ACEI only (38 [6.0%] on generic lisinopril and the remaining 66 [10.4%] on other generic and brand ACEIs); 320 (50.6%) on other monotherapy including 119 (18.8%) on beta-blocker, 88 (13.9%) on calcium channel blocker, 73 (11.6%) on diuretic; and 40 (6.3%) on other drugs such as alpha-blockers (e.g., doxazosin, terazosin).

‡ Mean and standard deviations were calculated for continuous variables. Chi-square test and Student’s t test were computed for testing the differences between groups, and a P value <0.05 was established as a statistically significant difference.

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; HCTZ = hydrochlorothiazide; HTN = hypertensive.

ARB, and reduce average antihypertensive drug therapy costs. The rate of attempted initiation of ARB versus ACEI therapy was lower for the health plans with this intervention than for the comparison group without the step-therapy intervention for ARBs (19.2% vs. 25.8%, respectively).

The step-therapy program did shift patients to other antihypertensive therapy as evidenced by 48.8% of patients (n=632) receiving an antihypertensive drug other than an ARB following the ARB claim rejection. About one third (192 of 632) of these patients received an ACEI alone or in some combination. The study also demonstrated that 6.6% of patients did not receive any antihypertensive therapy within 12 months of a rejected ARB claim. Furthermore, of the 1,296 patients who attempted to get ARB therapy, 578 (44.6%) received an ARB as initial therapy (via PA), but only as monotherapy in 233 patients. Over time, 323 patients who initially received other antihypertensive therapy switched to or added ARB therapy within 12 months, for a total of 901 patients (69.5%) who received an ARB within 12 months of the first attempt.

Our findings are similar to other studies that evaluate the impact of step-therapy programs. Compared with our cost savings of 13% per day of antihypertensive drug therapy, Dunn et al. found a 9% cost savings per day of antidepressant drug therapy associated with a step-therapy intervention for generic antidepressants, other than tricyclic antidepressants, before coverage of a brand-name antidepressant. Analysis of a step-
Effects of a Step-Therapy Program for Angiotensin Receptor Blockers on Antihypertensive Medication Utilization Patterns and Cost of Drug Therapy

The step-therapy program for COX-2 inhibitors suggested that up to 70% of patients did not attempt to obtain a PA after their claim for a COX-2 was rejected at the point of sale.\textsuperscript{10} A step-therapy edit for proton pump inhibitors or nonsteroidal anti-inflammatory drugs found that 44% of patients received a different medication than was originally prescribed and 11% received no medication.\textsuperscript{16} The 11% of patients who received no therapy is greater than the 6.6% of patients in our study who did not receive any antihypertensive therapy after the step-therapy claim rejection. Besides variations in patient demographics and other key factors, the methodologies used in assessing the percentage of patients not receiving any therapy after step edit differed. Our study evaluated medication use 12 months after the step edit via pharmacy claims while the proton pump inhibitor/nonsteroidal anti-inflammatory drug study by Cox et al. used a cross-sectional patient survey, without analysis of actual pharmacy claims, that included questions on why patients might not have received their medication.\textsuperscript{10}

While most patients continued with ACEI or other antihypertensive therapy following the rejected ARB attempt in the current study, the step-therapy program delayed the time for some patients to receive a (higher-cost) ARB, resulting in cost reduction for the 3 health plans where the step-therapy program was in place. Of the patients who received other antihypertensive therapy following the rejected ARB attempt, more than 50% switched to or added an ARB within 12 months.

The cost of therapy as measured by mean drug ingredient cost per patient was lower in the step-therapy group than in the overall comparison group, producing an unadjusted antihypertensive drug cost savings of $75.12 ($445.12 minus $370.00) per patient per year. Ordinary least squares regression analysis showed that the edit was associated with a $43.91 ingredient cost savings per patient over 12 months (Table 7). This difference in the descriptive savings of $75.12 per patient per year compared with $43.91 determined by regression analysis appears to be attributable to the “healthier” population in the intervention group that was younger and had a lower average severity of illness (CDS) score. This translates into approximately $298,000 in savings in 1 year, or $0.025 PMPM across the 1 million health plan members.

Although PA and step-therapy programs are generally effective at reducing direct drug costs, more research is needed on other outcomes, including medical use and costs and humanistic outcomes such as member and provider satisfaction.\textsuperscript{5, 11} This is the first study to examine the impact of a pharmacy step-therapy program for managing the use and costs of ARB therapy. The use of rejected and paid claims data in this analysis, compared with PA data only, allows for identification of cost savings associated with ARB claims avoided or delayed as a result of the step-therapy program. We identified those patients who encountered a rejected claim for an ARB and followed them for 12 months. While we do not know which patients attempted to get a PA or did not attempt to get a PA but were denied, we identified the antihypertensive therapy and associated costs in the 12-month follow-up period.

**Limitations**

First, while the study population was large, which provided adequate sample size to examine the distribution of patients as antihypertensive treatment changed over the follow-up period, the current study included only pharmacy claims data, so the effect of the step-therapy intervention on clinical outcomes such

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Step-Therapy Group*</th>
<th>Comparison Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attempted and Received an ARB (n = 578) % (n)</td>
<td>Attempted an ARB and Received Other Antihypertensive Therapy (n = 632) % (n)</td>
<td>Started on an ACEI (n = 5,462) % (n)</td>
</tr>
<tr>
<td>Switched to/added ARB by 3 months</td>
<td>–</td>
<td>35.6 (223)</td>
</tr>
<tr>
<td>Switched to/added ARB by 6 months</td>
<td>–</td>
<td>43.2 (273)</td>
</tr>
<tr>
<td>Switched to/added ARB by 12 months</td>
<td>–</td>
<td>51.1 (323)</td>
</tr>
<tr>
<td>Switched to/added ACEI by 12 months</td>
<td>5.7 (33)</td>
<td>–</td>
</tr>
</tbody>
</table>

* An additional 86 patients in the step-therapy group did not receive any antihypertensive therapy in the 12 months following the initial rejected claim for an ARB.

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker.
as blood pressure control and/or attainment of JNC 7 therapy goals is unknown. Second, we did not measure service outcomes that included member and provider satisfaction. Third, we were not able to assess why physician prescribing patterns were different between the intervention and comparison groups, and particularly why the prevalence of ACEI/ARB prescribing was nearly 3 times greater in the comparison group than in the intervention group. If this rate of prescribing ACEIs and ARBs is associated with some sort of “sentinel” effect, then the cost savings from this ARB step-therapy intervention are underestimated in the current study.

Fourth, while this was a “smart” step-therapy edit that did not simply reject the ARB claim and require the pharmacy provider to resolve the claim rejection, this intervention did result in 45% of affected patients receiving an ARB through PA. We did not measure the pharmacy and prescriber costs associated with requesting PA or changing drug therapy to an ARB alternative. We also did not assess administrative costs or the resources required to operate this intervention, and therefore could not calculate a return on investment from this managed care intervention. Other than program operation costs, some costs likely were incurred in physician office visits to switch or titrate therapy as well as pharmacy costs associated with explaining claim rejections to patients. Fifth, this study did not include the potential effects of rebate contracts on drug costs, which could offset some of the cost savings from the step-therapy intervention.

Our findings suggest that the step-therapy intervention for managing the use and cost of ARB therapy reduced the number of patients who were initially prescribed and received an ARB. However, we did identify patients who switched to or added an ARB within 12 months of the initial rejection in addition to those patients who were approved for ARB therapy at the time of application. While the drug cost savings were substantial from this step-therapy intervention, some of the savings would be consumed by program administrative costs and possible therapy interruption or disruption, including the 6.6% of patients who did not receive antihypertensive drug therapy after their initial ARB claims were rejected at the point of service.

**Conclusions**

A step-therapy intervention for ARBs (including ARB-HCTZ combinations) that required prior use of an ACEI or an ARB (including HCTZ combinations) was associated with an approximately 13% lower drug cost per day compared with a health plan with no step-therapy intervention. For the 3 health plans with this managed care intervention, the 1-year drug cost savings were about $368,000, or $0.03 PMPM across the approximately 1 million members. The administrative costs to implement and operate this ARB step-therapy intervention were estimated to be small but were not measured, and any costs that might be incurred in the form of either member or provider dissatisfaction or pharmacist and physician time were also not measured.
**TABLE 7** Regression Analysis: Impact of ARB Step Therapy on Ingredient Cost per Patient Over a 12-Month Period

<table>
<thead>
<tr>
<th>Variable</th>
<th>Definition</th>
<th>Unstandardized Coefficients ($)</th>
<th>Standardized Coefficients ($)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step therapy</td>
<td>Step therapy = 1</td>
<td>-43.909</td>
<td>-0.040</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age</td>
<td>Years</td>
<td>-1.125</td>
<td>-0.036</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gender</td>
<td>Female = 1</td>
<td>-7.350</td>
<td>-0.009</td>
<td>0.007</td>
</tr>
<tr>
<td>Chronic Disease Score</td>
<td>See Methods section</td>
<td>0.004</td>
<td>0.022</td>
<td>0.001</td>
</tr>
<tr>
<td>Average copay per Rx per member for all drugs during 1 year</td>
<td>Dollars</td>
<td>5.094</td>
<td>0.121</td>
<td>0.001</td>
</tr>
<tr>
<td>Average no. of 30-day anti-HTN Rxs per patient during 1 year</td>
<td>Total days supply for anti-HTN drugs/30 days</td>
<td>27.533</td>
<td>0.732</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Dependent variable = ingredient cost per patient per 12 months.
N = 40467
R² = 0.561
HTN = hypertensive, Rx = prescription.

**What is already known about this subject**

- Step-therapy interventions are common in managing population costs for medical care and pharmacy services.
- ARBs are higher in direct drug cost compared with ACEIs, which are widely available generically.
- There is a need to measure the impact of step-therapy programs for ARBs due to the limited availability of information in the literature.

**What this study adds**

- A step-therapy intervention for ARBs conducted in 3 large health plans that required prior use of an ACEI or ARB was associated with significant direct drug cost savings, but administrative costs and clinical or service outcomes were not measured.

**ACKNOWLEDGMENTS**

Jeff White, PharmD, MS, director, Clinical Analytic Strategies, WellPoint NextRx, West Hills, CA, contributed to the regression analysis and manuscript revisions.

**DISCLOSURES**

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Yokoyama served as principal author of the study. Study concept and design were contributed by all authors. Data collection was the work of Yokoyama, with input from Yang; data interpretation was the work of all authors. Writing of the manuscript was the work of Yokoyama, with input from Preblick; its revision was the work of all authors.

**REFERENCES**

Effects of a Step-Therapy Program for Angiotensin Receptor Blockers on Antihypertensive Medication Utilization Patterns and Cost of Drug Therapy


ABSTRACT

BACKGROUND: Before the introduction of the immunomodulatory therapies for multiple sclerosis (MS), treatment options for MS consisted of symptomatic management (physical therapy and pharmacological treatment for symptom management). Symptomatic management for MS has been supplemented in the past decade by 2 new classes of immunomodulatory therapies that have been approved as first-line treatments for relapsing-remitting multiple sclerosis (RRMS): subcutaneous glatiramer acetate (SC GA) and 3 β-interferons: intramuscular interferon β-1a (IM IFNβ-1a), SC IFNβ-1a, and SC IFNβ-1b.

OBJECTIVE: To estimate the economic outcomes of 5 treatment strategies: symptom management alone, symptomatic management combined with SC GA, IM IFNβ-1a, SC IFNβ-1a, or SC IFNβ-1b in patients diagnosed with RRMS.

METHODS: A literature-based Markov model was developed to assess the cost-effectiveness of 5 treatment strategies for managing a hypothetical cohort of patients diagnosed with RRMS in the United States—4 immunomodulatory drug therapies and symptomatic management alone. Health states were based on the Kurtzke Expanded Disability Status Scale (EDSS), a widely accepted scale for assessing RRMS (higher EDSS scores = increased disease severity). Baseline relapse and disease progression transition probabilities for symptom management were obtained from natural history studies. Treatment effects of the immunomodulatory therapies were estimated by applying a percentage reduction to the symptom management transition probabilities for relapse (27% reduction) and disease progression (50% reduction). Transition probabilities were subsequently adjusted to account for (1) the effects of neutralizing antibodies, specifically on relapse rates by assuming no additional therapy benefits after the second year of continuous therapy, and (2) treatment discontinuation. Therapy-specific data were obtained from clinical trials and long-term follow-up observational studies. Transitions among health states occurred in 1-month cycles for the lifetime of a patient.

RESULTS: The incremental cost per quality-adjusted life-year for the 4 immunomodulatory therapies is $258,465, $303,968, $416,301, and $310,691 for SC GA, IM IFNβ-1a, SC IFNβ-1a, and SC IFNβ-1b, respectively, compared with symptom management alone. Sensitivity analyses demonstrated that results were sensitive to changes in utilities, disease progression rates, time horizon, and immunomodulatory therapy cost.

CONCLUSIONS: The pharmacoeconomic model determined that SC GA was the best strategy of the 4 immunomodulatory therapies used to manage MS and resulted in better outcomes than symptom management alone. Sensitivity analyses indicated that the model was sensitive to changes in a number of key parameters, and thus changes in these key parameters would likely influence the estimated cost-effectiveness results. Head-to-head randomized clinical trials comparing the immunomodulatory therapies for the treatment of MS are necessary to validate the projections from the pharmacoeconomic analyses, particularly since the results available today from the clinical trials do not account adequately for treatment dropouts.

KEYWORDS: Multiple sclerosis, Immunomodulatory therapy, Markov model, Cost-effectiveness

J Manag Care Pharm. 2007;13(3):245-61
**TABLE 1**
Table of Immunomodulatory Therapy Clinical Trials in Relapsing-Remitting Multiple Sclerosis

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<td>for 6 months)</td>
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(continued on next page)
Before the immunomodulatory therapies for MS were introduced, treatment options for MS consisted of symptomatic management (physical therapy and pharmacological treatment for symptom management). Symptomatic management for MS has been supplemented in the past decade by 2 new classes of immunomodulatory therapies that have been approved as first-line treatments for RRMS: subcutaneous glatiramer acetate (SC GA) (Copaxone) and 3 β-interferons: intramuscular interferon β-1a (1M IFNβ-1a [Avonex]), SC IFNβ-1a (Rebif), and SC IFNβ-1b (Betaseron). Evidence from randomized clinical trials (1-2 years12-19; prospective extensions of the clinical trials (2-5 years)20-23; and long-term follow-up studies of patients initially enrolled in clinical trials24-27 (one of which extends beyond 10 years28) have shown that there is good evidence demonstrating the benefits of immunomodulatory therapies in reducing relapse rates, slowing the progression of disability, and reducing MS disease activity (Table 1).

However, the use of the immunomodulatory therapies in everyday clinical practice has been a topic of substantial debate. The National Institute for Clinical Excellence (NICE) determined

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**Table 1** Table of Immunomodulatory Therapy Clinical Trials in Relapsing-Remitting Multiple Sclerosis (continued)

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<td>35 months (77.6%)</td>
<td>Mean number of relapses over 2 years: GA: 1.19 PLA: 1.68 RR (vs. PLA): GA = 0.71</td>
<td>Annual relapse rate (all patients): 30 µg: 0.67 PLA: 0.82 RR (vs. PLA): 30 µg = 0.82 Annual relapse rate (2-year completers): 30 µg: 0.61 PLA: 0.90 RR (vs. PLA): 30 µg = 0.68</td>
<td>Relapse rate over 2 years: 30 µg: 0.77 PLA: 0.81 Annual relapse rate over 2 years: 22 µg: 1.82 44 µg: 1.73 RR (vs. PLA): 22 µg = 0.71 44 µg: 0.68</td>
<td>N/A Time (months) to progression of disability (increase of 1.0 point on EDSS sustained for 6 months): 30 µg: 13.7 PLA: 0.67 Time (months) to progression of disability (increase of 1.0 point on EDSS sustained for 3 months): 22 µg: 18.5 44 µg: 21.3 PLA: 11.9</td>
<td>Annual relapse rate over 2 years: 1.6 MIU: 1.17 8 MIU: 0.84 PLA: 1.27 RR (vs. PLA): 1.6 MIU = 0.92 8 MIU = 0.66</td>
<td>N/A Relapse-free patients after 2 years: 1.6 MIU: 23% 8 MIU: 36% PLA: 18%</td>
<td>Relapse-free patients after 24 weeks: 44 µg: 75% 30 µg: 63% Relapse-free patients after 48 weeks: 44 µg: 62% 30 µg: 52%</td>
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<td>6 years (61.6%)</td>
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<td>8 years (57.6%)</td>
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<td>10 years (51.2%)</td>
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</table>

CIMSSG = Copolymer-1 Multiple Sclerosis Study Group; DB = double blind; EDSS = Expanded Disability Status Scale (Kurtzke); EIFNBDCS = European IFNβ-1a Dose-Comparison Study; EVIDENCE = Evidence of Interferon Dose-Response: European North American Comparative Efficacy; GA = glatiramer acetate; IFN = interferon; IFNBMSGG = Interferon Beta Multiple Sclerosis Study Group; IM = intramuscular; INCOMIN = Independent Comparison of Interferon; ITT = intent to treat; LTFU = long-term follow-up visit; MIU = million international units; MRI = magnetic resonance imaging; MS = multiple sclerosis; MSCRG = Multiple Sclerosis Collaborative Research Group; N/A = not available; N/R = not reported; PLA = placebo; PRISMS = Prevention of Relapses and Disability by interferon Beta-1a Subcutaneously in Multiple Sclerosis; RCT = randomized clinical trial; RR = relative risk; SC = subcutaneous; µg = micrograms.
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that “...on the balance of their clinical and cost-effectiveness, neither beta interferon nor glatiramer acetate is recommended...” and those therapies were provided to patients only after the Department of Health and the respective manufacturers agreed to a risk-sharing scheme. In contrast to NICE's guidance, some clinical practice guidelines have recommended the immunomodulatory therapies for the treatment of MS. The selection of specific therapies is based on individual patient characteristics (e.g., disease severity, patient compliance) and treatment characteristics (e.g., efficacy, incidence of neutralizing antibodies [NAbs], side effects).

The socioeconomic burden of MS is substantial given the debilitating nature of this chronic, progressive, and lifelong condition that affects individuals in the most productive years of life. Drug acquisition cost for the immunomodulatory therapies was estimated to exceed $16,000 per patient per year in 2006, a significant expenditure for health care payers. The annual cost of illness of MS (in 1994 US$) is estimated to be between $6.8 and $13.6 billion, composed largely of indirect costs for formal/informal care and lost earnings. Patwardhan et al. assessed the link between disability levels and costs and found that costs rose at an exponential rate with increasing MS disability levels, a finding that was consistent with previously published studies. Given this evidence of increasing costs (direct and indirect) with increasing disease severity, we believe the ability of the immunomodulatory therapies to reduce relapse rates and slow the progression of the MS may assist in reducing resource use and may, in turn, help to offset the cost of these therapies.

Cost-effectiveness and cost-utility analyses (CEA/CUAs) are useful tools to assess the tradeoff between the added costs and potential benefits (e.g., improved patient outcomes) of new therapies. In the current environment of cost-consciousness and limited health care resources, CEA/CUA affords decision makers an opportunity to evaluate new therapies from an economic perspective and quantify the budgetary implications of adopting such therapies. A majority of the published CEA/CUA evaluations of immunomodulatory therapies for MS have been conducted from perspectives outside the United States. In a recent U.S.-based CUA evaluation, immunomodulatory therapy for the treatment of nonprimary, progressive MS (e.g., RRMS and SPMS) was compared with no treatment over a 10-year time horizon. Cost-effectiveness results from this analysis, as well as previously published CUA evaluations, were considerably higher than the arbitrary and commonly referenced benchmark of $50,000 per quality-adjusted life-year (QALY).

Recent published literature on the impact of the immunomodulatory therapies in MS has provided key data that have not been previously used in CEA/CUA evaluations. Specifically, long-term follow-up data of patients initially enrolled in clinical trials have been published, one of which, for SC GA, extended beyond 10 years. In previous CEA/CUA evaluations, long-term treatment outcomes (e.g., treatment effects and discontinuation rates) were extrapolated over time based primarily on data from short-term clinical trials. In addition to long-term follow-up data, there has been focus on the development of NAbs among patients prescribed beta-interferons, which may inhibit or “neutralize” the effectiveness of beta-interferon treatment.

Because of data limitations, previous models have made assumptions regarding the impact of beta-interferons on treatment effects (e.g., constant treatment effects over time), which, in turn, made it difficult to examine the impact that NAbs might have on cost-effectiveness. With the availability of long-term data, cost-effectiveness analysis of various therapies in the presence of these clinical markers can be made more appropriately. In this regard, we examine the cost-effectiveness of 5 treatment strategies in patients diagnosed with RRMS (symptom management alone and in combination with SC GA, IM IFNβ-1a, SC IFNβ-1a, or IM IFNβ-1b). Cost-effectiveness results (symptom management vs. the 4 immunomodulatory therapies) were reported in terms of cost per QALY gained as well as cost per outcome achieved.
(e.g., cost per year spent relapse free or cost per year spent in less severe disease health states), thus providing decision makers relevant data with which to evaluate the cost-effectiveness of the 4 immunomodulatory therapies versus symptom management in treating RRMS.

## Methods

### Model Description

We developed a Markov model to assess the cost-effectiveness of 5 treatment strategies to manage a hypothetical cohort of patients diagnosed with RRMS in the United States. The strategies were symptom management alone (e.g., physical therapy/exercise and pharmacological treatment [e.g., corticosteroids for relapse, tizanidine for spasticity, and modafinil for fatigue]) and symptom management in combination with 1 of the following immunomodulatory therapies: SC GA, IM IFNβ-1a, SC IFNβ-1a, or SC IFNβ-1b. The clinical course of RRMS (e.g., disease progression and relapse) was modeled in terms of the Kurtzke Expanded Disability Status Scale (EDSS). Specifically, 7 EDSS health states were modeled (Figure 1):

1. EDSS 0.0-2.5: no or few limitations in mobility
2. EDSS 3.0-5.5: moderate limitations in mobility
3. EDSS 6.0-7.5: walking aid or wheelchair required
4. EDSS 8.0-9.5: restricted to bed
5. Death (natural causes or EDSS 10)
6. Relapse EDSS 0.0-2.5: relapse with a change in disability within EDSS 0.0-2.5
7. Relapse EDSS 3.0-5.5: relapse with a change in disability within EDSS 3.0-5.5

Transitions among the health states occurred in 1-month cycles. The baseline time horizon of the model was assumed to be lifetime in order to capture the full benefits of immunomodulatory therapy. Costs and outcomes were estimated from the societal perspective and were discounted at 3% per annum. All costs were reported in 2005 U.S. dollars. The natural history of MS disease progression, clinical efficacy of MS therapies, mortality, resource use, costs, and utilities were obtained from the published literature. The model calculated the following outcomes: average number of years spent in EDSS 0.0-5.5; average number of years spent relapse free; life-years; QALYs; total costs and costs by component (i.e., immunomodulatory therapy cost, MS-related medical costs [e.g., drugs for symptom management], and lost worker productivity costs); and incremental cost-effectiveness ratios comparing symptom management alone with symptom management combined with each of the 4 immunomodulatory therapies. Model parameters were varied in sensitivity analyses.

A number of underlying assumptions were adopted for the base-case model:

1. A Web survey of patients (aged ≥18 years) treated with immunomodulatory therapy in the United States and enrolled in a patient support program was used to determine the percentage of patients entering the model among the 4 nonrelapse EDSS health states (Table 2). The survey, based on previous surveys conducted in the United States and Europe, was completed by 711 MS patients and collected data such as disease information (e.g., type of MS, therapy used), quality of life, resource use, and associated costs (direct and indirect). The majority of surveyed patients were in the lower EDSS health states (e.g., EDSS ≤6.0), which represents RRMS patients eligible for immunomodulatory therapy, and the overall distribution was relatively consistent with previously published surveys among patients diagnosed with MS. Sensitivity analyses were conducted to assess varying patient distributions (e.g., 100% of patients start in EDSS 0.0-2.5 health state).

2. The point at which patients transformed from RRMS (characterized by clearly defined relapses with at least partial recovery of deficits and lack of disease progression between relapses) to SPMS (characterized by less frequent relapses and deficits that begin to progress even between relapses) was not specified in the model, as the precise time at which this transformation takes place is not clearly defined. Rather, the model assumed that this transformation took place between EDSS 3.0-5.5 and EDSS 6.0-7.5. Corresponding to this assumption, the model assumed that relapses occurred only in patients in the lower EDSS health states (EDSS 0.0-5.5) and that the rate of disease progression increased in the higher EDSS health states (EDSS 6.0-9.5).

3. The model assumed that, per product labeling, only RRMS patients were eligible for and received immunomodulatory therapy, corresponding to patients in the lower EDSS health states (i.e., EDSS 0.0-5.5).

4. Switching among the immunomodulatory therapies was not permitted in the model. Patients discontinuing immunomodulatory therapy were assigned the transition probabilities for relapse and disease progression used in the symptom management arm. Patients who discontinued therapy were not permitted to reinitiate therapy.

5. The model assumed that nonrelapse-related EDSS scores do not improve over time; therefore, patients transitioned to the next, more severe health state, 1 health state at a time, corresponding to a progression in disease severity (e.g., EDSS 0.0-2.5 to EDSS 3.0-5.5).

The base-case parameter inputs, values, and additional assumptions are detailed in the next sections and are summarized in Table 2.

### Clinical Course of MS

Relapse and disease progression transition probabilities within the symptom management arm were obtained from published natural history studies (relapse rates, disease progression, as reported in a previous MS cost-effectiveness model). Mortality due to natural causes was assumed to occur at any cycle in the model based on age-specific, all-cause mortality rates. Mortality due to MS was assumed to occur only after patients had progressed through all EDSS health states.
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(i.e., only patients in the EDSS 8.0-9.5 health state could transition to EDSS 10, which is death). This assumption was consistent with a previous model that was based on data indicating that nearly 90% of MS patients were significantly disabled (e.g., unable to walk) before death. These data are presented in Table 2.

### Treatment Effects of SC GA and the β-Interferons

Treatment effects associated with the immunomodulatory therapies were estimated by adjusting (via a percentage reduction) the probabilities of relapse and disease progression used in the symptom management arm of the model. Relapse and disease progression rates over time were obtained from randomized clinical trials (SC GA, IM IFNβ-1a, SC IFNβ-1b, SC IFNβ-1a, SC IFNβ-1b); prospective extensions of the clinical trials (SC GA, IM IFNβ-1a, SC IFNβ-1a, SC IFNβ-1b); and long-term follow-up studies (SC GA, SC IFNβ-1a).

Relapse and disease progression rates were then mapped and fitted to prediction curves over time to estimate the long-term treatment effects of SC GA and the β-interferons (relapse: Figure 2; disease progression: Figures 3 and 4).

To account for the inherent differences between the randomized clinical trials (e.g., patient population, primary endpoint), a fixed patient population was assumed for the base-case model. In particular, all patients entered the model on the basis of a fixed EDSS distribution (Table 2). Furthermore, short-term outcomes were modeled by assuming, for all immunomodulatory therapies, a single percentage reduction for relapse and disease progression in the first 2 years of therapy (Table 2). This assumption was based on data from several published review papers that indicated annual relapse and disease progression rates in the randomized clinical trials were similar among therapies. In subsequent years of the model, treatment effects were estimated based on the long-term, immunomodulatory-specific prediction
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Curves. Sensitivity analyses were performed to assess the impact of varying the percentage reduction adjustments.

To account for the effect of NAbS, the probabilities of relapse for patients in the β-interferon arms of the model were subsequently adjusted. The model assumed that NAbS would affect the probability of relapse and would occur only after the second year of continuous interferon treatment. The incidence of NAbS was obtained from the published literature and was used to calculate an adjusted probability of relapse that reflected a weighted average of NAb+ (NAb+) and NAb- (NAb-) patients. A conservative approach to modeling the impact of NAbS was adopted, where NAb+ patients (titer ≥20) experienced a probability of relapse equal to that of the year-2 probability in each subsequent year of the model, and NAb- patients experienced a probability of relapse equal to that predicted by the fitted curve described previously. The model did not consider dose escalation of the β-interferons in response to NAbS.

The probabilities of relapse (adjusted for NAbS) and disease progression associated with the immunomodulatory therapies were also adjusted to account for patients who discontinued therapy. Rates of discontinuation were obtained from the published clinical trials and long-term follow-up studies; a relative 3% annual discontinuation rate was assumed in the event data were not available. Patients who discontinued therapy were assigned the probabilities of relapse and disease progression used in the symptom management arm of the model. Similar to the calculation performed for NAbS, the adjusted probability of relapse and disease progression reflected a weighted average of patients continuing and discontinuing therapy. The fitted curves for the long-term treatment effects of the immunomodulatory therapies adjusted for NAbS and discontinuation are reflected in Figures 2-4. The figures indicate an immediate short-term reduction in relapse and disease progression rates and a stabilization in rates (relapse and disease progression) over the long term.

### Table 2: Summary of Parameters and Values Used in the Base-Case Markov Model (continued)

<table>
<thead>
<tr>
<th>Parameter Description</th>
<th>Estimate for Base-Case Model</th>
<th>Range for Sensitivity Analysis (±25% Unless Indicated Otherwise)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Health state-specific MS-related costs (monthly)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EDSS 0.0-2.5</td>
<td>$433.26</td>
<td>$324.95-$541.58</td>
<td>Oleen-Burkey [abstract]</td>
</tr>
<tr>
<td>EDSS 3.0-5.5</td>
<td>$838.83</td>
<td>$629.12-$1,048.54</td>
<td></td>
</tr>
<tr>
<td>EDSS 6.0-7.5</td>
<td>$1,990.02</td>
<td>$1,492.52-$2,487.53</td>
<td></td>
</tr>
<tr>
<td>EDSS 8.0-9.5</td>
<td>$3,499.59</td>
<td>$2,624.69-$4,374.49</td>
<td></td>
</tr>
<tr>
<td>Relapse EDSS 0.0-2.5</td>
<td>$427.98</td>
<td>$320.99-$534.97</td>
<td></td>
</tr>
<tr>
<td>Relapse EDSS 3.0-5.5</td>
<td>$1,094.80</td>
<td>$821.10-$1,368.50</td>
<td></td>
</tr>
<tr>
<td>Monthly cost of lost worker productivity (no. of days missed x hourly wage x % of patients employed)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptom management</td>
<td>$154.74</td>
<td>N/C</td>
<td>$116.06-$193.43</td>
</tr>
<tr>
<td>SC GA</td>
<td>$109.39</td>
<td>$84.94-$133.82</td>
<td>$82.05-$136.74</td>
</tr>
<tr>
<td>IM IFNβ-1a</td>
<td>$167.40</td>
<td>$158.04-$176.77</td>
<td>$125.55-$209.26</td>
</tr>
<tr>
<td>SC IFNβ-1a</td>
<td>$167.40</td>
<td>$158.04-$176.77</td>
<td>$125.55-$209.26</td>
</tr>
<tr>
<td>SC IFNβ-1b</td>
<td>$162.63</td>
<td>$159.47-$165.79</td>
<td>$121.97-$203.29</td>
</tr>
<tr>
<td>Utility weights</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EDSS 0.0-2.5</td>
<td>0.824</td>
<td>0.618-1.000</td>
<td>0.710</td>
</tr>
<tr>
<td>EDSS 3.0-5.5</td>
<td>0.679</td>
<td>0.509-0.849</td>
<td>0.590</td>
</tr>
<tr>
<td>EDSS 6.0-7.5</td>
<td>0.533</td>
<td>0.400-0.666</td>
<td>0.420</td>
</tr>
<tr>
<td>EDSS 8.0-9.5</td>
<td>0.491</td>
<td>0.368-0.614</td>
<td>0.125</td>
</tr>
<tr>
<td>Utility decrement associated with relapse</td>
<td>0.094</td>
<td>0.071-0.118</td>
<td>N/C</td>
</tr>
</tbody>
</table>

**Note:** EDSS = Expanded Disability Status Scale (Kurtzke); EDSS 0.0-2.5 = no MS symptoms to minimal disability in 2 functional areas; EDSS 3.0-5.5 = moderate disability in 1 functional area or mild disability in up to 4 areas to disability severe enough to preclude full daily activities; EDSS 6.0-7.5 = intermittent or unilateral constant assistance required to walk 100 meters to wheelchair; EDSS 8.0-9.5 = restricted to bed with many self-care functions retained to requiring assistance for all activities of daily living; GA = glatiramer acetate; IFN = interferon; IM = intramuscular; MS = multiple sclerosis; N/A = not applicable; NAb = neutralizing antibodies; N/C = no change; SC = subcutaneous; symptom management = symptomatic management alone; WAC = wholesale acquisition cost.
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Costs

The model accounted for immunomodulatory therapy acquisition costs, health state-specific MS-related medical costs, and the cost of lost worker productivity. Costs were obtained from the published literature and were inflated to 2005 U.S. dollars, where necessary, by the medical component of the Consumer Price Index. The annual acquisition cost of SC GA and each β-interferon was calculated using wholesale acquisition costs (WACs), days supply per prescription, the recommended dosing schedule, patient compliance (assumed 70% in base-case model), patient copayment ($25 per prescription in base-case model), and the proportion of patients discontinuing therapy as reported in clinical trials (see Table 1).

Health state-specific MS-related medical costs were estimated from the previously described Web survey of 711 RRMS patients in the United States. The resource use and associated costs component of the survey was used in the model and comprised the cost of inpatient care, outpatient care, community services, alterations and equipment, informal care, and medications used to manage the symptoms of MS. Costs were estimated on the basis of Current Procedural Terminology, 4th Edition (CPT-4) codes and corresponding physician fees for each CPT-4 code, diagnosis-related groups, and the Drug Topics Red Book (WAC prices). Health state and drug costs are presented in Table 2.

Worker Productivity

Estimates of lost worker productivity were based on the published literature. Specifically, Lichtenberg estimated the average number of days missed from work for 47 major chronic conditions, including MS. SC GA and β-interferon-specific estimates of the number of days missed from work (all reasons) were derived via regression analyses of retrospective administrative claims data and were subtracted from the Lichtenberg baseline value to determine the average number of days missed due to MS for each therapy. The cost of lost worker productivity was estimated as the number of work days missed (in hours) multiplied by an hourly wage and adjusted to account for the proportion of patients employed (Table 2).

The model assumed that productivity losses were limited to patients in EDSS 0.0-5.5 and that patients in the later EDSS health states (EDSS >5.5) were not employed. Since the results of the Lage et al. analysis identified a modest nonsignificant difference in work days missed for the β-interferons relative to no treatment, the base-case model took these modest differences into account even though they were not statistically significant by using the conservative assumption that the absolute reduction in days lost from work was incurred in comparison with symptom management. Furthermore, while providing an estimate of absenteeism (within the context of a small sample size and including paid time off [PTO]), the Lage et al. analysis did not provide an estimate of overall lost worker productivity, which includes both absenteeism (lost productivity associated
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with missing a work day, excluding PTO) and presenteeism (lost productivity associated with being present at work but performing below expectations). The results reported by Lage et al. provided an estimate of presenteeism that, given the lack of better data, might be used in the model to estimate the impact of MS and its treatments on worker productivity.

Utilities
Utility weights allow an objective measurement of the desirability of a health state. Utility weights range from 0.0 to 1.0, where a utility value of 1.0 represents perfect health and a value of 0.0 represents death. These utility values are used to estimate QALYs by multiplying the number of life-years within a particular health state by that health state's utility weight. Utilities were estimated by health state and were obtained from the published literature (Table 2). The relapse health states were associated with a 0.094 decrement in utility (e.g., utility for relapse EDSS 0.0-2.5 = 0.824 – 0.094 = 0.730).

Model Calculations
The model estimated the following outcomes: average number of years spent in EDSS 0.0-5.5; average number of years spent relapse free; life-years; QALYs; and total costs and costs by component (i.e., immunomodulatory therapy cost, MS-related medical costs, and lost worker productivity costs). Incremental cost-effectiveness ratios (ICERs) were assessed in the model by comparing each of the individual immunomodulatory therapies plus symptomatic management with symptom management. The ICERs were calculated as the difference in costs between 2 treatments divided by the difference in effectiveness: (Cost Drug A – Cost Drug B) / (Effectiveness Drug A – Effectiveness Drug B). The resulting ICERs described the relative cost of purchasing 1 additional unit of relative effectiveness (e.g., cost of 1 additional year spent in the lower EDSS health states). ICERs were calculated for 4 effectiveness measures (cost per QALY; cost per life-year; cost per year spent in the lower EDSS health states [EDSS 0.0-5.5]; and cost per year spent relapse free).

Sensitivity Analyses
To test the robustness of the model assumptions and specific parameters, univariate sensitivity analyses were performed by increasing and decreasing values for key parameters in the model. Plausible ranges of values were obtained from the published literature or by varying the estimates by up to 25% in each direction. Parameters analyzed included health state and relapse state utilities; symptomatic treatment costs, health state costs, and drug costs; percentage employed and work days saved; percentage reductions in relapse and disease progression rates in the first 2 years of therapy; changes in relapse and disease progression over time; change in treatment discontinuation over time; EDSS distribution; incidence of NAbs; change in NAbs over time; and discount rates. Sensitivity results for each model input assessed were ranked from most sensitive to least sensitive and plotted on a tornado diagram. Results (Figure 5) indicated that changes in health state utilities were the most sensitive model parameter. To further test the sensitivity of the model to changes in health state utilities, 3 analyses were performed: (1) changing all utility values by a relative ±25%; (2) replacing the utility values in the base-case model with European-derived utilities used in previous economic evaluations; and (3) changing only the disutility values associated with the relapse health states by a relative ±25%. Additional scenario-based sensitivity analyses were performed to evaluate the impact on model results of changes to multiple parameters (e.g., simulating assumptions used in previously published MS models). Ranges used in sensitivity analyses (univariate and scenario) are presented in Table 2.

Results
Total costs per patient over the time horizon of a patient’s lifetime were estimated at $295,586, $352,760, $364,267, $377,996, and $358,509 for symptom management, SC GA, IM IFNβ-1b, SC IFNβ-1a, and SC IFNβ-1b, respectively (Table 3). MS-related medical costs were the largest cost component (approximately 95% of total costs in the symptom management arm and 70%-75% of total costs in the immunomodulatory arms), followed by the cost of immunomodulatory therapy (approximately
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Figure 5: Sensitivity Analyses Results

Sensitivity analyses were based on two methods of changing values: (1) by +25% and -25%, and (2) by prespecified values. The gray bars present results from method #1 and the white bars represent results from method #2. The asterisks are specific to the white bars:

* Time horizon: base case = lifetime; sensitivity analysis = 5 years.
** Compliance: base case = 70%; sensitivity analysis = 100%.
*** Utility values: base case = U.S.-based values; sensitivity analysis = European-based values.
**** EDSS distribution: base case = across all EDSS health states; sensitivity analysis = all patients start in first EDSS health state (EDSS 0.0-2.5).

EDSS = Expanded Disability Status Scale (Kurtzke); GA = glatiramer acetate; IFN = interferon; IM = intramuscular; MS = multiple sclerosis; NAbs = neutralizing antibodies; SC = subcutaneous.
20%-25% of total costs). Comparing direct medical costs (i.e., MS-related medical costs and immunomodulatory therapy costs) of the symptom management arm with the SC GA, IM IFNβ-1a, SC IFNβ-1a, and SC IFNβ-1b arms of the model (from Table 3), we found the added cost of immunomodulatory therapy was partially offset by savings in MS-related medical costs, and the greatest cost offsets occurred in the SC GA arm (24% of the cost of SC GA was offset by savings in MS-related medical costs versus 17%-22% of the cost of the β-interferons).

Outcomes over the lifetime time horizon assessed in the model were similar across the 4 immunomodulatory therapies and were generally improved compared with outcomes with symptom management (Table 3). The exception was for the estimated life-years gained, as immunomodulatory therapy had little impact on survival other than the slight delay in disease progression to EDSS 10 (death). Comparisons among the 4 immunomodulatory therapies indicated that patients on SC GA had slightly better outcomes relative to patients on the β-interferons.

Overall, the model indicated that patients on SC GA experienced greater cost benefits compared with patients on any of the 3 β-interferons. The incremental cost per QALY was $258,465, $337,968, $416,301, and $310,691 for SC GA, IM IFNβ-1a, SC IFNβ-1a, and SC IFNβ-1b, respectively, compared with symptom management. ICERs comparing symptom management with the 4 immunomodulatory therapies for the other outcomes of interest are presented in Table 3.

Sensitivity Analyses

Overall, univariate sensitivity analyses showed results to be sensitive to changes in health state utilities, the percentage reduction in disease progression rates in the first 2 years of therapy used to estimate immunomodulatory therapy treatment effects, model time horizon, and immunomodulatory therapy acquisition costs (Figure 5). Further assessment of changes to health state utilities revealed that changes to the disutility values associated with the relapse health states had minimal effect on cost-effectiveness results. However, changes to utility values over all health states had a substantial impact. We observed the greatest impact when we changed all utility values by a relative ±25%.

In a scenario in which the model assumed no change in SC GA effects on disease progression in the first 2 years and a 25% improvement for the β-interferons, we observed an overall improvement in the cost-effectiveness of the β-interferons compared with symptom management, and the ICERs for the β-interferons (vs. symptom management) were more favorable than those of SC GA (vs. symptom management). However, ICERs for the β-interferons (vs. symptom management) did not improve compared with SC GA (vs. symptom management) when we assumed no change in SC GA effects on relapse in the first 2 years and a 25% improvement for the β-interferons. As expected, shorter time horizons (e.g., 10-20 years) resulted in larger ICERs when we compared symptom management with each of the 4 immunomodulatory therapy arms of the model, as the shorter time horizons did not fully account for all benefits associated with immunomodulatory therapy. Assuming no change in the acquisition cost of SC GA and a 25% decrease in the acquisition cost of the β-interferons resulted in more favorable ICERs for the β-interferons (vs. symptom management) compared with SC GA (vs. symptom management). Finally, changes in the incidence of NAbs had minimal impact on the ICERs of the β-interferons compared with symptom management.

Discussion

The present analysis is the first economic model in MS to (1) incorporate long-term data on treatment effects, (2) include the effect of NAbs on the β-interferons, (3) account for the inherent differences among clinical trial study designs of the immunomodulatory therapies (e.g., via fixed EDSS distribution and single percentage reduction in relapse and disease progression rates in the first 2 years of therapy), and (4) present results in terms of cost-utility (cost per QALY gained) and cost-effectiveness (e.g., cost per year spent relapse free or cost per year spent in less severe disease health states). Model results highlight the potential long-term health and economic benefits of treating MS patients with immunomodulatory therapy and indicate that all 4 immunomodulatory therapies are associated with increased benefits compared with symptom management, albeit at higher costs and without consideration of the cost of adverse events. The model indicated that, of the 4 immunomodulatory therapies used to manage MS and in comparison with symptom management, SC GA was the best strategy in terms of outcomes and costs. Sensitivity analysis indicated that the model was sensitive to changes in a number of key parameters, and thus changes in these key parameters would likely influence the estimated cost-effectiveness results.

In a previous U.S.-based cost-effectiveness model conducted by Prosser et al., the authors concluded that IM IFNβ-1a compared with no treatment (i.e., symptomatic treatment) yielded the largest gain in QALYs with an ICER between $1.8 and $2.2 million per QALY gained. These results were significantly different from that reported in the current analysis and can be attributed to the underlying methodology used to model MS, the most notable aspects of which include assumptions regarding the treatment effects associated with the immunomodulatory therapies, model time horizon, and utility values. In terms of the treatment effects of the immunomodulatory therapies over time, the Prosser model is based on relapse rates and disease progression rates reported in the pivotal clinical trials for the respective drugs. The current analysis supplements the pivotal clinical trials with data from patients initially enrolled in the pivotal trials and followed over time. While both approaches have limitations (pivotal trials in MS are based on a 2-year
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### Table 3: Base-Case Discounted Costs per Patient (Lifetime Perspective)

<table>
<thead>
<tr>
<th>Cost Component</th>
<th>Symptom Management</th>
<th>SC GA</th>
<th>IM IFNβ-1a</th>
<th>SC IFNβ-1a</th>
<th>SC IFNβ-1b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lifetime drug acquisition costs (average no. of years on therapy)</td>
<td>$0</td>
<td>$77,340</td>
<td>$82,635</td>
<td>$95,208</td>
<td>$76,957</td>
</tr>
<tr>
<td>(N/A)</td>
<td>(13.54)</td>
<td>(13.05)</td>
<td>(12.93)</td>
<td>(13.21)</td>
<td></td>
</tr>
<tr>
<td>MS-related medical costs</td>
<td>$282,950</td>
<td>$264,351</td>
<td>$265,366</td>
<td>$266,839</td>
<td>$265,940</td>
</tr>
<tr>
<td>Productivity costs</td>
<td>$12,636</td>
<td>$11,069</td>
<td>$16,266</td>
<td>$15,948</td>
<td>$15,611</td>
</tr>
<tr>
<td>Total costs</td>
<td>$295,586</td>
<td>$352,760</td>
<td>$364,267</td>
<td>$377,996</td>
<td>$358,509</td>
</tr>
<tr>
<td>Average no. of years spent in EDSS 0.0-5.5</td>
<td>12.28</td>
<td>14.92</td>
<td>14.71</td>
<td>14.29</td>
<td>14.54</td>
</tr>
<tr>
<td>Average no. of years spent relapse-free*</td>
<td>11.42</td>
<td>14.67</td>
<td>14.24</td>
<td>13.98</td>
<td>14.15</td>
</tr>
<tr>
<td>Incremental cost per year spent in EDSS 0.0-5.5</td>
<td>–</td>
<td>$21,667</td>
<td>$28,293</td>
<td>$41,008</td>
<td>$27,860</td>
</tr>
<tr>
<td>Incremental cost per year spent relapse-free</td>
<td>–</td>
<td>$17,599</td>
<td>$24,327</td>
<td>$32,207</td>
<td>$23,065</td>
</tr>
<tr>
<td>Incremental cost per life-year gained</td>
<td>–</td>
<td>$2,076,622</td>
<td>$2,588,087</td>
<td>$3,378,626</td>
<td>$2,452,616</td>
</tr>
<tr>
<td>Incremental cost per QALY gained</td>
<td>–</td>
<td>$258,465</td>
<td>$337,968</td>
<td>$416,301</td>
<td>$310,691</td>
</tr>
</tbody>
</table>

* Cumulative number of months spent relapse-free converted to years.

GA = glatiramer acetate; IFN = interferon; IM = intramuscular; MS = multiple sclerosis; N/A = not applicable; QALY = quality-adjusted life-year; SC = subcutaneous; symptom management = symptomatic management alone.

A snapshot of a chronic, lifelong condition, and the follow-up studies are nonrandomized, they represent alternative methods for modeling MS outcomes. It should be noted that the published estimate of effectiveness for IM IFNβ-1a is based on those subjects who completed 2 years in the trial at the time it was stopped as opposed to being based on the intent-to-treat population. This approach likely overestimates the true effects of IM IFNβ-1a in this particular trial, which is apparent in results from head-to-head clinical trials of IM IFNβ-1a.18,19

Sensitivity analyses conducted in the Prosser model, the current analysis, and other MS models have clearly indicated that results are influenced by time horizon, with shorter time horizons associated with less favorable ICERs (e.g., Prosser18 and other models30,39,78) and longer time horizons associated with more favorable ICERs (e.g., current analysis, Nuijtten and Hutton41). Guidelines for the conduct of cost-effectiveness analyses (e.g., Academy of Managed Pharmacy,79 Canadian Coordinating Office for Health Technology Assessment,80 NICE81) recommend that pharmacoeconomic models should be sufficiently long to reflect all relevant costs and outcomes, which would suggest that an MS model should adopt a lifetime perspective, given the chronic nature of MS. While guidelines may suggest that a longer time horizon is more appropriate, the managed care perspective often reflects much shorter time horizons (e.g., 1-3 years), which would translate into increasingly less favorable ICERs as the time horizon is shortened. However, as the enrollment base of managed care plans shifts over time, plans are likely to gain and lose MS patients across the spectrum of disability levels. Thus, therapies that reduce relapse and disease progression rates, such as the immunomodulatory therapies for MS, may reduce the burden of MS.

A comparison of the utility values used in the current analysis with that of the Prosser model indicated substantial differences, which are reflected in the ICER results of the individual models. Utilities used in the Prosser model were derived from a U.S. sample of MS patients and members of the general community82 and were significantly higher than those reported in a subsequent U.S. study,83,84 which were used in the current analysis. The higher utilities contributed to the higher ICERs reported in the Prosser model. The Prosser utilities were also significantly higher than those reported in a subsequent U.K. study,85,86 which were used in the current analysis. The higher utilities contributed to the higher ICERs reported in the Prosser model. The Prosser utilities were also significantly higher than those reported in the United Kingdom and Europe87,88 (e.g., utility assigned to the initial EDSS health state 0.0-2.5 was 0.95 in the Prosser model compared with 0.71 derived from a European population for the same health state89), which is reflected in the more favorable ICERs calculated in analyses from other countries.30,40,41 It is also of interest that the percentage reduction in utilities from one health state to the next was smaller in the Prosser U.S.-based analyses (e.g., 9% reduction in utilities from EDSS 0.0-2.5 to EDSS 3.0-5.5 and 12% reduction in utilities from EDSS 3.0-5.5 to EDSS 6.0-7.546,52,77) compared...
with analyses performed in other countries that estimated a 30% reduction in utilities from EDSS 0.0 to EDSS 3.0 and a similar reduction from EDSS 3.0 to EDSS 7.0.30,78

Overall, the majority of economic evaluations in MS, including the current analysis, resulted in ICERs well above the arbitrary and commonly referenced benchmark of $50,000 per QALY, even in the “best-case” scenarios used in sensitivity analyses.30,40-46,78,83 This was, in part, a reflection of (1) the chronic nature of the disease, (2) survival not being significantly affected by the disease, (3) the modest QALY benefits associated with immunomodulatory therapy in MS versus symptom management, and (4) the high drug acquisition costs of the immunomodulatory therapies. A review of the published cost-effectiveness literature revealed a number of analyses of health care interventions that resulted in ICERs above the $50,000 per QALY benchmark, including $1.8 to $2.2 million per QALY as reported in the Prosser MS model86; $91,000 per QALY for osteoarthritis or rheumatoid arthritis patients using diclofenac versus ibuprofen84; $110,000 per QALY for patients using metformin in a diabetes prevention program85; $200,000 per QALY for osteoarthritis or rheumatoid arthritis patients using diclofenac and a proton pump inhibitor versus celecoxib86; $370,000 per QALY for women with irritable bowel syndrome using alosetron versus no treatment84; and $56,000 to $840,000 per QALY for the use of high-dose erythropoietin versus normal dosages to maintain increased hemoglobin levels (e.g., 12-14 g/dL).87

A review of the cost-effectiveness literature for blood safety interventions (e.g., blood screening and pathogen inactivation) identified a median ICER of $355,000 per QALY69 with some results exceeding several million dollars per QALY.69 While direct comparisons between these studies and the current analysis are limited, the results indicate that not all economic evaluations are bounded by the $50,000 per QALY benchmark and that numerous interventions with ICERs well above this threshold have been deemed valuable by patients, health care decision makers, and society. Thus, evaluating the cost-effectiveness of the immunomodulatory therapies in terms of the $50,000 per QALY benchmark may not be appropriate.

Limitations

First and foremost among the limitations of this study is its reliance on clinical trial data. While clinical trial data are considered the preferred source for the basis of parameter inputs used in cost-effectiveness analyses, the MS clinical trials have been criticized for a number of methodological issues. For example, in the Cochrane review of the β-interferon randomized, placebo-controlled clinical trials,83 Rice et al. commented that the quality of the trials was variable with substantial methodological inadequacies. In its review of all immunomodulatory therapy randomized clinical trials for MS, which included SC GA,29 NICE noted similar methodological issues concerning randomization,30,40 allocation concealment,30,36,40 intent-to-treat analysis,30,37,40 and last observation carried forward analysis.36 Finally, incomplete description of treatment dropouts in the short-term clinical trials likely affected trial results, where if dropouts were deemed to progress (worst-case scenario), the effect of these drugs on relapse and disease progression rates would likely be lost.85

Second, our economic analyses did not include the impact of adverse events (e.g., cost and disutility) except to the extent that these might be captured indirectly in the proportion of patients who discontinue therapy (Table 1). However, the cost of treating adverse events would not likely affect the overall results of this analysis since the most common adverse events reported for all 4 immunomodulatory therapies were injection site reactions and influenza-like symptoms, which were generally self-limiting and significantly decreased over time.90,91 Nevertheless, these adverse events would likely have an impact on patient utilities, which would influence the cost-effectiveness results. In the Prosser model, treatment-specific disutilities were assigned to account for patient discomfort associated with each treatment, where values ranged from 0.066 for SC GA to 0.204 for SC IFNβ-1b. These disutilities favored SC GA over the β-interferons and thus would not likely have changed the model results.

A third limitation arises from the assumption in the model that patients who discontinued immunomodulatory therapy were not allowed to switch to another therapy nor reintiate therapy at a later time. It is expected that a proportion of patients will discontinue therapy due to worsening of MS symptoms (e.g., as specified by the Association of British Neurologists’ guidelines for stopping therapy: 2 disabling relapses within 12 months, secondary progression with increased disability over 6 months, and loss of ability to walk that persists for 6 months32); however, some patients may discontinue therapy and experience no change in their disability status. On the basis of general clinical practice patterns, these patients would be likely candidates for switching or reinitiating therapy. Had patients been allowed to switch or reintiate therapy in the model, the calculated ICERs would likely be less favorable for all the immunomodulatory therapies. This assumption (no switching and no reintiation of therapy) was also adopted in other MS models.30,40,41,46 Evidence from real-world observational studies in MS has indicated that from 5%73,93 to 13% of patients72 switched therapy upon discontinuation.

A fourth limitation arises from the assumption in the model regarding the estimation of relapse and disease progression rates associated with the immunomodulatory therapies. To account for differences in the immunomodulatory clinical trials, a fixed patient population was assumed to enter the model (e.g., based on fixed EDSS distribution), and in the first 2 years of therapy, the model assumed that the probabilities of relapse and disease progression used in the symptom management arm were adjusted by a common percentage reduction (relapse: 27%;
disease progression: 30%). A fitted prediction curve of treatment effects was used to estimate long-term treatment effects of the immunomodulatory therapies. This is a conservative approach to modeling treatment effects over time that uses both the clinical trial and long-term data to predict future outcomes. Previous CEA/CUA studies for the immunomodulatory therapies relied on data from short-term clinical trials and made assumptions to extrapolate treatment effects over time. At the time of the present economic analyses, SC GA was the only immunomodulatory therapy with long-term data collected in a systematic manner over more than 10 years (although it is important to note that by 10 years, 51.2% of patients eventually withdrew from study follow-up). Thus, the fitted prediction curve for SC GA may be a better representation of patient outcomes compared with the curves estimated for the β-interferons, which were based on significantly shorter time horizons (e.g., the longest follow-up was 6 years for SC IFN-β1a).

Fifth, the data used in the present economic analysis are not from comparative, head-to-head clinical trials of the immunomodulatory therapies. Comparative trials of this type, particularly one in which all 4 therapies were evaluated head to head, would be the ideal source of information for the model, but the similarity in outcomes across the 4 therapies suggests that a very large and expensive randomized clinical trial would be necessary in order to observe significant differences among the therapies. Nevertheless, reviews of the individual randomized clinical trials for the 4 immunomodulatory therapies suggest that the therapies have similar short-term effects on relapse and disease progression rates.

Sixth, clinical trials are designed to specifically test the efficacy and tolerability of a particular therapy in a select patient population. The specified inclusion and exclusion criteria of clinical trials may not result in a population that is representative of all patients (e.g., real-world situations). This is especially relevant in MS clinical trials in which patients are selected on the basis of a number of criteria, including having experienced an average of 2 relapses in the previous 2 years, a rate that is relatively higher than that reported for the general MS population (range of 0.14 to 1.1 relapses per year). From the modeling perspective, the clinical trial population is the best available data; however, cost-effectiveness results based on data derived from this population may or may not comport with population-based care and the projection of average economic costs.

### Conclusions

All 4 immunomodulatory therapies used in the treatment of RRMS patients are associated with increased benefits compared with symptom management alone, albeit at higher costs. The pharmacoeconomic model indicated that, of the 4 immunomodulatory therapies used to manage MS and in comparison with symptom management, SC GA was the best strategy. Sensitivity analysis indicated that the model was sensitive to changes in a number of key parameters, and thus changes in these key parameters would likely influence the estimated cost-effectiveness results. While the results of this analysis provide decision makers with health economic information supporting the use of the immunomodulatory therapies, MS is a heterogeneous disease and physicians must select the most appropriate treatment based on the disease characteristics of individual patients. Comparative head-to-head, randomized clinical trials of the immunomodulatory therapies for the treatment of MS are needed to confirm the results predicted by economic models.

### What is already known about this subject

- A number of CEA/CUA evaluations of the immunomodulatory therapies for MS have been published. However, the majority of these evaluations have been conducted from perspectives outside the United States. The most recent U.S.-based analysis was the recent CUA evaluation of the immunomodulatory therapies for the treatment of nonprimary, progressive MS (e.g., RRMS and SPMS) over a 10-year time horizon. Cost-effectiveness results from this analysis, as well as previous evaluations, were considerably higher than the arbitrary and commonly referenced benchmark of $50,000 per QALY.

### What this study adds

- The present analysis is the first economic model in MS to (1) incorporate long-term data on treatment effects, (2) include the effect of NAbS on the β-interferons, (3) account for the inherent differences among clinical trial study designs of the immunomodulatory therapies, and (4) present results in terms of cost-utility (cost per QALY gained) and cost-effectiveness (e.g., cost per year spent relapse free).

- Compared with the U.S.-based model published by Prosser et al. in 2004, the results from the present analysis are significantly different from that reported by Prosser and can be attributed to the underlying methodology used to model MS, the most notable aspects of which include assumptions regarding the treatment effects associated with the immunomodulatory therapies, model time horizon, and utility values.

### DISCLOSURES

Funding for this research was provided to RTI-Health Solutions by Teva Neuroscience, Inc., and was obtained by authors Christopher Bell, Jonathan Graham, and Stephanie Earnshaw Bell, Graham, and Earnshaw are employed by RTI-Health Solutions, an independent contract research organization that has received research funding from Teva Neuroscience, Inc., for this and other studies and from other pharmaceutical companies that market drugs for the treatment of patients with multiple sclerosis and other medical conditions. Authors MerriKay Oleen-Burkey and Jane Castelli-Haley are employed by Teva Neuroscience, Inc., which manufactures glatiramer acetate. Kenneth Johnson serves as a consultant to Teva Neuroscience, Inc. Oleen-Burkey discloses that she owns stock options in Teva Neuroscience, Inc., as well as stock in Pfizer and other health care companies.

Bell served as principal author of the study. Study concept and design were contributed primarily by Bell and Earnshaw, with input from the coauthors. Data collection was the work of Graham, Castelli-Haley, and Bell, with input from Oleen-Burkey and Earnshaw; data interpretation was the work of Johnson, and Earnshaw with input from the coauthors. Writing of the manuscript was primarily the work of Bell, Oleen-Burkey, and Castelli-Haley; with input from Earnshaw and Graham; its revision was the work of Bell, Graham, and Johnson, with input from the coauthors.
REFERENCES


Cost-effectiveness of Four Immunomodulatory Therapies for Relapsing-Remitting Multiple Sclerosis: A Markov Model Based on Long-term Clinical Data

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Actuarial Analysis of Private Payer Administrative Claims Data for Women With Endometriosis

David Mirkin, MD; Catherine Murphy-Barron, FSA, MAAA; and Kosuke Iwasaki, FIAJ, MAAA

ABSTRACT

BACKGROUND: Endometriosis is a painful, chronic disease affecting 5.5 million women and girls in the United States and Canada and millions more worldwide. The usual age range of women diagnosed with endometriosis is 20 to 45 years. Endometriosis has an estimated prevalence of 10% among women of reproductive age, although estimates of prevalence vary greatly. Endometriosis is the most common gynecological cause of chronic pelvic pain, but published information on its associated medical care costs is scarce.

OBJECTIVE: The aim of this study was to determine (1) the prevalence of endometriosis in the United States, (2) the amount of health care services used by women coded with endometriosis in a commercial medical claims database during 1999 to 2003, and (3) the endometriosis-related costs for 2003, the most recent data available at the time the study was performed.

METHODS: This study was a retrospective review of administrative data for commercial payers, which included enrollment, eligibility, and claims payment data contained in the Medstat Marketscan database for approximately 4 million commercial insurance members. All claims and membership data were extracted for each woman aged 18 to 55 years who had at least 1 medical or hospital claim with a diagnosis code for endometriosis (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] codes 617.00-617.99) for 1999 through 2003. Claims data from 1999 through 2003 were used to determine prevalence and health care resource utilization (i.e., annual admission rate, annual surgical rate, distribution of endometriosis-related surgeries, and prevalence of comorbid conditions). The cost analysis was based on claims from 2003 only.

RESULTS: The prevalence of women with medical claims (inpatient and/or outpatient) containing ICD-9-CM codes for endometriosis was 1.1% for the age band of 30 to 39 years and 0.7% over the entire age span of 18 to 55 years. The medical costs per patient per month (PPPM) for women with endometriosis were 63% greater ($706 PPPM) than those of the average woman per member per month ($433) in 2003; inpatient hospital costs accounted for 32% of total direct medical costs. Between 1999 and 2003, these women with endometriosis who were identified by either inpatient and/or outpatient claims had high rates of hospital admission (53% for any reason; 38% for an endometriosis-related reason) and a high annual surgical procedure rate (64%). Additionally, women with endometriosis frequently suffered from comorbid conditions, and these conditions were associated with greater PPPM costs of 16% to 50% for women with an endometriosis diagnosis code, depending on the condition. Interstitial cystitis was associated with 50% greater cost ($1,061 PPPM); depression, 41% ($997 PPPM); migraine, 40% ($986 PPPM); irritable bowel syndrome, 34% ($943 PPPM); chronic fatigue syndrome, 29% ($913 PPPM); abdominal pain, 20% ($846 PPPM); and infertility, 15% ($813 PPPM).

CONCLUSIONS: Women with endometriosis have a high hospital admission rate and surgical procedure rate and a high incidence of comorbid conditions. Consequently, these women incur total medical costs that are, on average, 63% higher than medical costs for the average woman in a commercially insured group.

KEYWORDS: Endometriosis, Chronic pelvic pain, Women’s health, Prevalence, Comorbidity, Resource utilization

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Endometriosis is a painful, estrogen-dependent gynecological condition that can be categorized as mild, moderate, or severe, and is defined as the presence of endometrial glands and stroma outside the uterine cavity and musculature. It is a long-term condition and usually lasts until menopause.

The clinical manifestations of endometriosis are variable and unpredictable and include secondary dysmenorrhea, worsening primary dysmenorrhea, dyspareunia, noncyclic lower abdominal pain, backache, uterosacral ligament nodularity, and adnexal mass. Interestingly, the stage and localization of pelvic endometriosis are not associated with the frequency of symptoms. The pathogenesis of the disease remains unclear, although leading theories suggest retrograde menstruation, hematogenous or lymphogenous transport, and coelomic metaplasia.

Menstruating women of any age or race can develop endometriosis, although the usual age range of women diagnosed with the condition is 20 to 45 years. The estimated prevalence of the disease is 10% among women of reproductive age, making it more common than diabetes in this population. A much higher prevalence occurs in women with chronic pelvic pain (CPP, 33%-82%), premenopausal women (50%), and in women undergoing investigation of infertility (21%). Indeed, endometriosis is the most common gynecological cause of CPP, a disabling condition responsible for 10% of hysterectomies and 40% of laparoscopies and affecting up to 40% of women receiving primary care. Other disorders associated with CPP are secondary muscular adaptations and psychological conditions, such as depression.

While no conclusive evidence supports endometriosis as a cause for infertility, there is general agreement that infertility is often associated with endometriosis and that anatomical distortion from endometriosis often causes infertility.

This disease usually becomes apparent in the reproductive years when the lesions are stimulated by ovarian hormones. However, endometriosis pain has little relationship to the site or color of lesions. Risk factors favoring endometriosis...
development include a shorter menstrual cycle, longer bleeding periods, and early menarche. Women who smoke and those who are overweight have a reduced risk of developing the condition. Despite recent advances, endometriosis is still difficult to diagnose and treat. Many women with CPP do not receive diagnostic testing, are never diagnosed, and are not referred to a specialist.

Endometriosis is often mistaken for other conditions that cause pelvic pain, such as pelvic inflammatory disease, ovarian cysts, or irritable bowel syndrome (IBS). Left undiagnosed or untreated, painful periods caused by endometriosis can lead to absenteeism from work and school and can strain relationships. Recurring pain can lead to depression, irritability, anxiety, anger, and feelings of helplessness. Infertility linked to endometriosis can also cause emotional distress.

The disease is associated with significant morbidity rates. Between 1990 and 1998, it was the third most common gynecological diagnosis listed in the hospital discharge summaries of women aged 15 to 44 years. Endometriosis results in lost productivity, hospitalizations, and surgical procedures, as well as outpatient and prescription drug costs. Many women resort to bed rest during bouts of endometriosis-related pain, with almost half the women with endometriosis in one study reporting the need for an average of 17.8 days of bed rest in the previous 12 months.

Note: HMO and EPO claims tend to be unreliable for determining cost and utilization rates because not all services are submitted as encounters, so utilization and cost can be underestimated. * Member-year = total days of eligibility divided by 365. † Allowed charges = net payer cost + member cost share.

EPO = exclusive provider organization; ER = emergency room; ESRD = end-stage renal disease; HMO = health maintenance organization; ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification; POS = point of service; PPO = preferred provider organization.
months as a direct result of endometriosis.23

The aims of endometriosis treatment are to eliminate symptoms, reduce the process of inflammation, and limit tissue destruction that might result from long-standing disease.4

Endometriosis can be treated effectively with medical therapy or surgery or both.5,24-26 Symptoms such as pain can be controlled with medical therapy alone, thus avoiding the need for surgery.5,24-26 Surgical treatment is considered second-line therapy, reserved for patients who have failed medical treatment or who have evidence of extensive disease.26 The American College of Obstetrics and Gynecology (ACOG) clinical practice guidelines2 for the medical treatment of endometriosis state that, for pain relief, treatment with a gonadotropin-releasing hormone (GnRH) agonist or with danazol appears to be effective in most women. The guidelines state that when pain relief is achieved by treatment with a GnRH agonist (thus endorsing continued therapy), the addition of add-back therapy reduces or eliminates GnRH-induced bone mineral loss without reducing the efficacy of pain relief. Therapy with a GnRH agonist is an appropriate approach to pain management in a woman with CPP, even in the absence of surgical confirmation of endometriosis, provided that a detailed initial evaluation fails to demonstrate some other cause of pelvic pain.2

Endometriosis-related hospitalizations and surgical procedures are a major burden on health care systems, but there is little information in the literature regarding the direct medical costs of endometriosis.27 Endometriosis-related surgery for women in the U.S. Army was associated with an average of 15 days of hospital and convalescent days per procedure.26 Others in the United States have reported average length of stay and hospital charges for endometriosis of 3.8 days and $6,597 in 1991 and 3.5 days and $7,450 in 1992, representing total annual charges of $504 million and $579 million, respectively.29

This study aimed to determine (1) endometriosis prevalence, (2) the volume and cost of health care services used by women coded with endometriosis during 1999 to 2003, and (3) endometriosis-associated costs for 2003 (the most recent data available at the time the study was performed). To our knowledge, this is the first study to report actuarial analysis of administrative data for women coded with endometriosis for private commercial insurance payers.

Methods

Data Source

This study was a retrospective review of payer administrative enrollment, eligibility, and claims payment data for women coded with endometriosis for 1999 through 2003, the most recent data available at the time the study was performed. This information was obtained from Milliman, Inc. (New York), which maintains proprietary medical claims databases, including the Medstat Marketscan database (Figures 1a, 1b). Milliman maintains administrative claim databases that link paid claims and encounter data that give detailed patient information across treatment sites and types of providers over time.

The Medstat Marketscan database contains all paid claims generated by roughly 4 million (male and female) commercially insured lives. Member identification codes are consistent from year to year and allow multiyear longitudinal studies. Information includes diagnosis codes; procedure codes and diagnosis-related grouping codes; national drug classification codes, together with site of service information; and the amounts paid by commercial insurers. These data were used to generate medical condition incidence rates and cost.

Database Inclusion/Exclusion Criteria

In this analysis, only commercial claims were reviewed for persons aged ≤65 years with employer-sponsored insurance categorized as basic/major medical (<1%), comprehensive (18%), point of service (28%), and preferred provider organization (54%). Health maintenance organization (HMO) and exclusive provider organization (EPO) claims were specifically excluded from our cost and utilization analysis (Figure 1a) since they include encounter data, (also called zero-dollar claims), which are not used to reimburse providers. HMO and EPO claims tend to be unreliable for determining cost and utilization rates because not all services are submitted as encounters, so utilization and cost can be underestimated.

The endometriosis population was a subset of the Medstat Marketscan database, using data for eligible persons with commercial claims.

Endometriosis Population

The endometriosis population was defined as women of childbearing age (18 through 55 years) with at least 1 of the following types of claims with an endometriosis diagnosis (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] codes 617.00-617.99):

- 1 inpatient claim
- 1 emergency room (ER) claim
- 2 outpatient claims (other than laboratory or radiology claims) on different dates, with endometriosis already identified

Once a woman was identified for the endometriosis population, all claims were assessed for that woman for the entire period in which she appeared as an eligible member. It was not required for a woman to be enrolled for the entire 5-year period. The database comprises actual employer data and is therefore subject to normal employee turnover.

Endometriosis Episode

Endometriosis is a chronic intermittent condition with no definitive endpoint. To perform the analysis, we needed to arbitrarily determine a time period during which a woman was deemed to have endometriosis and was potentially receiving treatment. In this study, we referred to this time period as the
“endometriosis episode.” An endometriosis episode was deemed to have started when a claim with an endometriosis diagnosis code was first made. The episode was deemed to have ended 12 months after the date of the last endometriosis claim or symptom. Women could thus be included in both the endometriosis population and the nonendometriosis population at some point within the 5-year period (sequentially). A woman was required to be a member for the full endometriosis episode time period (i.e., a minimum of 12 months) in order to be included in the endometriosis population analysis. Adnexal pain (ICD-9-CM code 625.9) and dysmenorrhea (ICD-9-CM code 635.3) were chosen as the symptoms of endometriosis; other symptoms, such as IBS or CPP, may or may not be related to endometriosis so were not used to determine endometriosis episodes.

Use of Benchmarks

Milliman’s Health Cost Guidelines were used for benchmarking the results found for the endometriosis population to the average adult female population. The guidelines are a database and a model used to provide a flexible but consistent basis for determining health claim costs and premium rates for a wide variety of health plans. The guidelines are developed from a number of claims databases, including Medstat Marketscan and other data sources that are proprietary to Milliman. These other data sources include private insurance companies and data vendors. Milliman’s Health Cost Guidelines are updated annually and are continually monitored. The standard demographics in the guidelines were developed using data from large insurers combined with Department of Labor sources to represent the age and sex distribution for a typical large insured group. These demographics are useful comparators to give an indication of the magnitude of difference between the endometriosis population and the average adult female population.

Actuarial Analyses

Actuaries work with insurers, HMOs, employers, and other clients to assign a financial value to future unknown health care events, such as endometriosis. They use standard mathematical and statistical techniques, including the law of large numbers, to analyze historical use and cost information and predict the use and cost of future contingent events. Actuarial analysis is the foundation for all types of insurance, and every insurance company relies on actuaries to estimate use, claims expense, and financial reserves and to set premium rates. Actuarial analyses were used throughout this study.

Prevalence and resource utilization rates were determined using member-years or member-months. “Member-year” was defined as total days of eligibility divided by 365. “Member-month” was defined as total days of eligibility divided by 30. Member-months were converted to member-years by dividing by 12. Member-years and member-months were therefore the actual years or months an individual was eligible for enrollment in a health insurance benefits program. Any particular individual might be enrolled for only part of a year, and using member-years or member-months accurately reflects that fact. For example, a woman eligible from January 1, 2002, through July 15, 2003, had 561 days of eligibility, 18.7 member-months, or 1.56 member-years.

Prevalence was calculated as the sum of member-years for the endometriosis population divided by the sum of member-years for all members.

Annual admission rate was calculated as the number of admissions divided by the sum of member-years for the endometriosis population.

Annual surgical rate was calculated as the number of surgical procedures divided by the sum of member-years during the endometriosis period for the endometriosis population.

Distribution of endometriosis-related surgical procedures was calculated as the sum of member-months for women with endometriosis and a comorbid condition divided by the sum of member-months for the endometriosis population. In this case, women were required to be enrolled for a minimum of 12 months, which would ensure an opportunity for a comorbidity to show up if one existed.

For resource utilization analyses, claims data were taken from the Medstat database from 1999 through 2003. The cost analysis was based on inpatient, outpatient, and prescription drug costs for the endometriosis population in 2003 only. That was the most recent year for which cost data were available. In addition, use of a single year’s data eliminated the need to adjust for trend from year to year.

Administrative claims data were grouped into 3 categories: inpatient, outpatient, and prescription drugs. Inpatient claims included care received at an inpatient facility and billed using a UB-92 claim form. This category included room and board and ancillary services, such as use of surgical and intensive care facilities, inpatient nursing care, pathology and radiology procedures, drugs, and supplies. It did not include professional charges unless performed by the staff of the facility. Outpatient claims included care received at an outpatient facility or a physician’s office and billed using a Health Care Financing Administration (HCFA)-1500 claim form. This category also included prescription drugs administered in the physician’s office, which were usually covered under a person’s medical insurance. The prescription drug category included all drugs obtained from a pharmacy, with the claims commonly processed through a pharmacy benefits manager.
Actuarial Analysis of Private Payer Administrative Claims Data for Women With Endometriosis

Statistical Analyses

Distribution of endometriosis-related surgeries and the prevalence of comorbid conditions in women coded with endometriosis were compared with the general female population using the $z$ test. The $z$ test was used instead of the more commonly used $t$ test because of the large numbers of women involved in the analyses, ranging from hundreds of thousands to millions. $P$ values ≤0.05 were judged to be significant.

Results

Prevalence of Endometriosis

In this study, the prevalence of endometriosis in administrative data collected between 1999 and 2003 was 0.7% (40,150 member-years), with the highest prevalence occurring in women aged 25 to 49 years (Table 1). Endometriosis prevalence varied slightly by U.S. geographic region, from a low of 0.5% for the western and eastern regions to a high of 0.7% for the southern, southeastern, and midwestern regions (data not shown).

<table>
<thead>
<tr>
<th>Age (Years)</th>
<th>Member-Years‡</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-19</td>
<td>552</td>
<td>0.2</td>
</tr>
<tr>
<td>20-24</td>
<td>2,159</td>
<td>0.4</td>
</tr>
<tr>
<td>25-29</td>
<td>4,160</td>
<td>0.9</td>
</tr>
<tr>
<td>30-34</td>
<td>7,486</td>
<td>1.1</td>
</tr>
<tr>
<td>35-39</td>
<td>8,621</td>
<td>1.1</td>
</tr>
<tr>
<td>40-44</td>
<td>8,141</td>
<td>0.9</td>
</tr>
<tr>
<td>45-49</td>
<td>5,804</td>
<td>0.6</td>
</tr>
<tr>
<td>50-54</td>
<td>2,923</td>
<td>0.3</td>
</tr>
<tr>
<td>55</td>
<td>304</td>
<td>0.1</td>
</tr>
<tr>
<td>Total</td>
<td>40,150</td>
<td>0.7</td>
</tr>
</tbody>
</table>

Data source: Medstat Marketscan administrative claims database.

* Prevalence was calculated as the sum of member-years for endometriosis population/sum of member-years for all eligible members.
† ICD-9-CM diagnosis codes for endometriosis: 617.00–617.99.
‡ Member year = total days of eligible membership divided by 365.


Costs for Women with a Diagnosis Code for Endometriosis

Significant expense was associated with women with an endometriosis diagnosis code. As shown in Figure 2, these women had total costs in 2003 of $706 per patient per month (PPPM) compared with $433 per member per month (PMPM) for the average woman. Women coded with endometriosis incurred higher inpatient, outpatient, and prescription drug costs (Figure 2). Outpatient costs, which include costs for physician, radiology, laboratory, and outpatient hospital services, represented the most expensive category for women coded with endometriosis (Figure 2).
### TABLE 2
2003 Charges* per Patient per Month (PPPM) for Women 1 and 2 Years Postdiagnosis Compared With Average 2003 Charges for Women With an Endometriosis Diagnosis Code†

<table>
<thead>
<tr>
<th></th>
<th>Average PPPM Charges 1 Year Postdiagnosis (n = 7,933 Member-Years) ($)</th>
<th>Average PPPM Charges 2 Years Postdiagnosis (n = 3,204 Member-Years) ($)</th>
<th>2003 Average Charges (% of Total Cost)§ (n = 30,235 Member-Years) ($)</th>
<th>Medical Charges for the Average Woman(§) ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inpatient</td>
<td>530</td>
<td>135</td>
<td>229 (32.4)</td>
<td>97</td>
</tr>
<tr>
<td>Outpatient</td>
<td>560</td>
<td>280</td>
<td>367 (52.1)</td>
<td>273</td>
</tr>
<tr>
<td>Prescription drug</td>
<td>120</td>
<td>115</td>
<td>110 (15.5)</td>
<td>62</td>
</tr>
<tr>
<td>Total average PPPM charge</td>
<td>1,210</td>
<td>530</td>
<td>706</td>
<td>433</td>
</tr>
</tbody>
</table>

Data source: Medstat Marketscan administrative claims database, 2003 allowed charge data.
* Charge = plan-allowed charge, i.e., net payer cost + member cost share.
† ICD-9-CM diagnosis codes for endometriosis 617.00–617.99.
§ Member-year = total days of eligible membership divided by 365.
¶ Plan-allowed charge for the average woman aged 18-55 years were derived from Milliman’s Health Cost Guidelines.

### TABLE 3
Age Distribution of Women With an Endometriosis Diagnosis Code Who Underwent Hospital Admissions Between 1999 and 2003

<table>
<thead>
<tr>
<th>Age (Years)</th>
<th>Annual Admission Rate for Any Reason* % (n)</th>
<th>Annual Admission Rate for an Endometriosis-Related Reason* % (n)</th>
<th>Rate of Endometriosis-Related Surgery† % (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-19</td>
<td>16 (88/552)</td>
<td>5 (29/552)</td>
<td>55 (244/440)</td>
</tr>
<tr>
<td>20-24</td>
<td>21 (454/2,159)</td>
<td>9 (204/2,159)</td>
<td>56 (929/1,657)</td>
</tr>
<tr>
<td>25-29</td>
<td>36 (1,486/4,160)</td>
<td>16 (674/4,160)</td>
<td>59 (1,978/3,322)</td>
</tr>
<tr>
<td>30-34</td>
<td>42 (3,129/7,486)</td>
<td>23 (1,731/7,486)</td>
<td>60 (3,784/6,287)</td>
</tr>
<tr>
<td>35-39</td>
<td>49 (4,239/8,621)</td>
<td>35 (2,975/8,621)</td>
<td>62 (4,525/7,346)</td>
</tr>
<tr>
<td>40-44</td>
<td>62 (5,054/8,141)</td>
<td>50 (4,071/8,141)</td>
<td>67 (4,585/6,886)</td>
</tr>
<tr>
<td>45-49</td>
<td>73 (4,233/5,804)</td>
<td>61 (3,564/5,804)</td>
<td>70 (3,395/4,877)</td>
</tr>
<tr>
<td>50-54</td>
<td>77 (2,241/2,923)</td>
<td>64 (1,866/2,923)</td>
<td>72 (1,784/2,473)</td>
</tr>
<tr>
<td>55</td>
<td>80 (2,44/304)</td>
<td>65 (199/304)</td>
<td>73 (193/265)</td>
</tr>
<tr>
<td>Overall % (total n)</td>
<td>53 (21,168/40,150)</td>
<td>38 (15,313/40,150)</td>
<td>64 (21,417/33,564)</td>
</tr>
</tbody>
</table>

Data source: Medstat Marketscan administrative claims database.
* Annual admission rate was calculated as the number of admissions divided by the sum of member-years for the endometriosis population in a given age distribution.
† Annual surgical rate was calculated as the number of surgeries during the endometriosis period divided by the sum of member-years during the endometriosis period for the endometriosis population in a given age distribution.
Endometriosis cohort = the number of member-years for women with endometriosis 1999–2003 (ICD-9-CM diagnosis codes for endometriosis: 617.00–617.99); n = 40,150 member-years.
Endometriosis-related surgery = endometriosis population with HMO and EPO data 1999-2003 and with at least 12 months continuous enrollment; n = 33,564 member-years. Member year = total days of eligibility divided by 365.
§ CPT-4 codes:
- Hysterectomy: 56308, 58150-58200, 58260-58294, 58546-58554
- Oophorectomy: 56307, 58940
- Laparotomy: 49000, 49010, 49200-49201, 58740, 58805, 58925
- Laparoscopy: 44200, 49320, 49321-49329, 56300-56306, 56309-56310, 58578, 58660-58679, 58800
- Endometrial ablation: 58563, 58563, 58353-58356

* ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification.
During the first year after diagnosis, women with an endometriosis diagnosis code had approximately 3-fold higher total medical costs compared with the average age-adjusted woman. Table 2 shows 2003 costs, by service category, for women coded with endometriosis who are in their first- and second-year postdiagnosis. Total medical costs for women with endometriosis were higher than average for the entire 2-year postdiagnosis period analyzed, with second-year costs being $530 PPPM in 2003.

For women coded with endometriosis, the mean annual hospital admission rate during the years 1999 to 2003 for any reason was 53% and for an endometriosis-related reason was 38% (Table 3). Sixty-four percent of women coded with endometriosis had an endometriosis-related inpatient or outpatient surgical procedure. The average time lost from work as a consequence was estimated as 13 days per procedure (data not shown). These days lost from work were not factored into the cost of endometriosis. Table 3 and Figure 3 show the hospital admission and surgical procedure rates by age for women coded with endometriosis.

Forty-three percent of women with an endometriosis diagnosis code during 1999 to 2003 underwent a major surgical procedure (such as hysterectomy, laparotomy, or oophorectomy). Indeed, 17% had 2 and 24% had 3 or more endometriosis-related surgeries. Thirty-one percent of women with an endometriosis code underwent hysterectomies, compared with an age-adjusted average of 1% for all women (P ≤0.001). Table 4 shows the distribution of endometriosis-related surgical procedures for women coded with endometriosis.

Women with an endometriosis diagnosis code had a significantly higher (P <0.001) incidence of claims for infertility, depression, migraine, interstitial cystitis (IC), IBS, chronic fatigue syndrome, and abdominal pain than the general adult female population (Table 5). The existence of these comorbid conditions with endometriosis was associated with greater PPPM costs, depending on the condition; IC contributing to a 50% increase in cost ($1,061 PPPM); depression, 41% ($997 PPPM); migraine, 40% ($988 PPPM); IBS, 34% ($943 PPPM); chronic fatigue syndrome, 29% ($913 PPPM); abdominal pain, 20% ($846 PPPM); and infertility, 15% ($813 PPPM) (Table 5).

**Discussion**

The results of this study showed that the prevalence of endometriosis determined from administrative data obtained between 1999 and 2003 was low (0.7%). Significant inpatient, outpatient, and prescription drug costs were incurred in 2003 by women with endometriosis ($706 PPPM) compared with the average commercially insured woman ($433 PMPM). These costs continued to be higher for the entire 2-year postdiagnosis period. In addition, between 1999 and 2003, women with endometriosis experienced high rates of endometriosis-related surgery (64%) as well as hospital admissions. Women coded with endometriosis frequently suffered from comorbid conditions, which increased costs by 15% to 50%, depending on the condition.

It is not surprising that the prevalence of endometriosis determined by clinical data is greater (10% vs. 0.7%) than the prevalence obtained from our administrative data. This finding implies that endometriosis is both underdiagnosed and undertreated. The ACOG management guideline estimates the prevalence of endometriosis as approximately 3% in women with CPP on the basis of evidence from 11 studies. However, within these studies, the reported prevalence of endometriosis varied widely, ranging from 2% to 74%. Such a large variation in prevalence rates raises the question of whether it is appropriate to use a single prevalence rate of endometriosis for all women with CPP.

Guo and Wang found identifiable sources of heterogeneity in prevalence estimates for endometriosis, with year of publication, sample size, and difference in evaluation of CPP being 3 apparent sources. Therefore, having a single prevalence rate estimate may be too simplistic. Insurer claims data show a much lower prevalence because not all cases of endometriosis will generate an interaction with the health care system and not all cases will
## TABLE 4

### Distribution of Endometriosis-Related Surgeries in Women With an Endometriosis Diagnosis Code Compared All Eligible Female Members (1999-2003)

<table>
<thead>
<tr>
<th>Type of Surgery</th>
<th>Women With an Endometriosis Diagnosis Code and a Surgical Procedure (% of 33,564 Member-Years)</th>
<th>All Women With This Surgical Procedure* (% of 7,144,896 Member-Years)</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hysterectomy</td>
<td>30.9</td>
<td>0.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Therapeutic laparoscopy</td>
<td>25.7</td>
<td>0.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diagnostic laparoscopy</td>
<td>7.6</td>
<td>0.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Laparotomy</td>
<td>6.6</td>
<td>0.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Oophorectomy</td>
<td>5.4</td>
<td>0.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Endometrial ablation</td>
<td>1.9</td>
<td>0.2</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data source: Medstat Marketscan administrative claims database.

* The all-women group consisted of the total population of eligible members between ages 18 and 55 years.
† Statistical test used = z test.

Endometriosis code cohort includes the number of member-years for women with endometriosis 1999–2003 (ICD-9-CM diagnosis codes for endometriosis: 617.00–617.99), including HMO and EPO claims. Distribution of endometriosis-related surgeries was calculated as the number of surgeries (defined by CPT-4 or ICD-9 code) divided by the sum of member-years during the endometriosis period for the endometriosis cohort population. Note: 41% of women had 2 or more endometriosis-related surgeries.

**Member year** = total days of eligibility divided by 365.

* CPT-4 codes:
  - Hysterectomy: 56308, 58150-58200, 58260-58294, 58546-58554
  - Oophorectomy: 56307, 58940
  - Laparotomy: 49000, 49010, 49200-49201, 58740, 58805, 58925
  - Laparoscopy: 44200, 49320, 49321-49329, 56300-56306, 56309-56310, 58578, 58660-58679, 58800
  - Endometrial ablation: 58563, 56356, 58353-58356

* ICD-9-CM codes:
  - Hysterectomy: 68.3-68.9
  - Oophorectomy: 65.3-65.64
  - Laparotomy: 65.89, 70.32, 57.59, 68.21, 68.29
  - Laparoscopy: 65.81, 54.21
  - Endometrial ablation: 68.23


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be coded or even recognized. It appears that only one quarter to one tenth of women with endometriosis are formally diagnosed and appropriately coded. This is common for conditions such as endometriosis, for which physicians tend to treat the symptoms rather than the condition itself. Endometriosis may often be missed because it is one of several underlying diseases causing CPP. Women with CPP are often evaluated, diagnosed, and treated according to the specialist directing their care. The cause of CPP remains undiagnosed for the majority of women. A definitive diagnosis of endometriosis requires direct visualization of ectopic endometrial lesions (usually via laparoscopy) accompanied by histological confirmation of the presence of at least 2 of the following features: hemosiderin-laden macrophages or endometrial epithelium, glands, or stroma. Therefore, most women with suspected endometriosis undergo surgery as part of their diagnostic workup. Diagnosis based solely on visual inspection requires a surgeon with experience in identifying the many possible appearances of endometrial lesions. Even so, there is poor correlation between visual diagnosis and confirmed histology. Additionally, deep endometriosis lesions (type III) can be easily missed clinically. There are currently no sufficiently sensitive and specific signs and symptoms or diagnostic tests for the clinical diagnosis of endometriosis, and no diagnostic strategy is supported by evidence of effectiveness. The risks and diagnostic limitations of laparoscopy and the inaccuracy of clinical examination have led to considerable efforts to improve diagnosis with imaging techniques. Unfortunately, imaging studies, such as ultrasonography or magnetic resonance imaging, do not show peritoneal disease or adhesions unless there are large endometriomas. In addition, although the specificity of cancer antigen (CA) 125 measurement has been reported as >85% with sensitivities between 20% and 50%, the clinical utility of measuring CA125 as a diagnostic marker for endometriosis appears to be limited.

Not surprisingly, women are frequently misdiagnosed. For example, in a British study of women with pelvic pain, many patients who eventually were diagnosed with endometriosis...
Delays in the diagnosis of endometriosis occur at an individual patient level and at a medical level, as both women and physicians normalize symptoms, suppress symptoms through hormones, and rely on nondiscriminatory investigations. Once diagnosed correctly, endometriosis is an expensive condition, with 2003 costs of $706 PPPM compared with $433 PMPM for the average commercially insured woman. The cost information reported in this study may be similar to previously published figures. For example, Zhao et al. published hospital charges for endometriosis of $6,597 in 1991 and $7,450 in 1992. Others have shown that estimated direct medical costs for outpatient visits for CPP for the U.S. population of women aged 18 to 50 years are $881.5 million per year. However, it is difficult to directly compare the results of the current study with previously published work. For instance, the results of Zhao et al. are based on hospital charge data or “billed charges,” which is the amount that a hospital bills a payer for services rendered. But this is not the amount paid by the health plan or the insurer because each payer has negotiated a payment rate with each hospital. This payment rate (allowed charge) is usually considerably less than the amount billed. The cost information in the current study is based on payer claims information and, as such, is the lower negotiated rate or “allowed charges.”

Whether measured by provider-submitted charges or allowed charges, the high cost incurred by women with endometriosis is due to the high rates of hospital admissions as well as surgical procedures and by the presence of significant comorbid conditions such as infertility, depression, and migraine. Interestingly, when 2004 endometriosis costs are extrapolated from 2003 figures using a 12% trend to account for inflation, the cost of endometriosis rises to $791 PPPM. This is similar or higher to previously and similarly calculated 2004 costs incurred for such high-profile conditions as hypertension ($500), diabetes ($916), and rheumatoid arthritis ($1,121) and is almost double the average 2004 medical costs for women ($485 PMPM). High rates of endometriosis-related surgery have been previously reported, with one case of a 36-year-old woman with a history of 11 surgical procedures related to pelvic pain or endometriosis over 20 years. Endometriosis requires histological confirmation, most commonly laparoscopy, for diagnosis. This and other gynecological surgical procedures have the potential for unexpected complications, such as blood loss and transfusion, bladder injury, pulmonary embolism, wound complications, and problems due to general anesthesia.

The high hospital and surgery rates observed in the current analysis are in line with these findings. In this study, women with endometriosis diagnosis codes had 35 times more hysterectomies and laparotomies and 20 times more oophorectomies compared...
with an age-adjusted average for all women.

The higher costs incurred by women with endometriosis might also be the result of the high incidence of serious comorbidities associated with this condition. The current analysis revealed that compared with the average for all women, women coded with endometriosis had more than 7 times the incidence of infertility, 4.5 times more IC, 2.5 times more IBS, 3 times more migraines and chronic fatigue syndrome, and 1.8 times more depression. Others have published similar results. For example, it has been previously estimated that between 30% and 50% of women with endometriosis are infertile\(^5\),\(^6\) and that as many as 86% of women suffering from endometriosis with CPP have depression.\(^1\)

Women with endometriosis also experience impaired health-related quality of life, especially in the domains of pain and psychological and social functioning.\(^3\),\(^1\) In the current study, the presence of these comorbidities increased costs by 15% to 50%, depending on the condition.

Gao et al.\(^2\) found that approximately 50% of endometriosis-related ambulatory patient visits involved specialist care and realized a need to coordinate services and treatment plans among specialists. Efforts should be undertaken to deliver more and better education on endometriosis and related conditions to all professionals providing health care to women. Health plans and employers should consider endometriosis to be one of the important high-cost chronic conditions deserving a focused disease management program similar to that developed for diabetes and rheumatoid arthritis.

Limitations

First and foremost among the limitations of this analysis is the reliance on accurate diagnosis and procedure coding in hospital and medical claims. Neither the hospital medical claims nor the eligibility data were audited for accuracy. Second, this analysis pertains only to the dataset of commercial health plans, excluding HMOs and EPOs. Third, we limited our analyses to adult women aged 18 to 55 years, which may underestimate the direct medical costs of endometriosis since Gao et al.\(^\) found that children and adolescents aged 10 to 17 years also account for endometriosis-related hospital admissions. A further underestimation may have resulted from the arbitrary determination of the length of an endometriosis episode because women might not have experienced any further endometriosis (and thus resource utilization) after their final coded event. Fourth, while we attempted to examine administrative claims data over a fairly wide time period (1999 through 2003), the definition of the inclusion criteria (i.e., an endometriosis ICD-9-CM code (617.00-617.99) on at least 1 inpatient claim or 1 ER claim or 2 outpatient claims other than laboratory or radiology claims) may have led us to overestimate the incidence of the rates of hospitalization and endometriosis-related surgical procedures and associated costs.

### Conclusions

Endometriosis diagnoses are associated with significant costs compared with women in the same age bands without these diagnosis codes. Specifically, this study found that endometriosis is expensive, with total costs in 2003 of $706 PPPM compared with $433 PMPM for the average woman. Endometriosis is a condition that is associated with frequent medical and surgical procedures and comorbidities.

### What is already known about this subject

- Endometriosis is a painful, long-term, estrogen-dependent gynecological condition that usually lasts until menopause.
- Endometriosis is difficult to diagnose and treat, contributing to difficulty in determining the economic burden of the disease.

### What this study adds

- This is the first study to report actuarial analysis of private (commercial insurance) payer administrative claims data for women coded with a diagnosis of endometriosis.
- The prevalence of endometriosis as actuarially derived from hospital and medical claims in adult women aged 18 to 55 years in a large commercial health insurance database was 0.7% overall and 1.1% for the age band 30 to 39 years.
- In the first 2 years after the initial diagnosis, women with endometriosis accounted for 63% greater direct medical costs compared with women without endometriosis diagnosis codes, $706 PPPM versus $433 PMPM in 2003 dollars.

### DISCLOSURES

Funding for this study was provided by TAP Pharmaceuticals Products, Inc., and was obtained by author David Mirkin. Mirkin and authors Catherine Murphy-Barron and Kosuke Iwasaki disclose no potential bias or conflict of interest relating to this article.

Mirkin served as principal author of the study. Study concept and design were contributed by all authors. Data collection was the work of Iwasaki, with input from Mirkin and Murphy-Barron; data interpretation was primarily the work of Murphy-Barron, with input from Mirkin. Writing of the manuscript was primarily the work of Mirkin, with input from Murphy-Barron; its revision was the work of Mirkin, with input from Murphy-Barron and Rx Communications, Ltd., Flintshire, United Kingdom.

### REFERENCES


Assessing Step-Therapy Programs: A Step in the Right Direction

Managed care organizations (MCOs) and pharmacy benefits managers (PBMs) use utilization management programs such as prior authorization (PA) and step therapy to improve the cost-effectiveness of therapeutic selection. Utilization management pharmacy benefit programs were first introduced in the 1980s and grew in popularity with the implementation of multiple-copayment (tiered) open formularies. Step therapy is appealing because it is generally applied to a select drug class with the goal of encouraging generic use and decreasing costs without compromising the quality of care.

Step therapy requires a member to try the first-line medication(s) within the drug class, usually a generic alternative, prior to receiving coverage for a second-line agent, usually a branded product. Currently, most PBMs implement step therapy using “smart edit” logic, and grandfathering those members who had received the target (second-line) drug previously. At the point of service, the “smart edit,” electronically and in real time, reviews the member’s claims history for evidence of use of first-line agent(s). If a claim is found, the system covers the second-line agent automatically. Otherwise, the claim is rejected. After claim rejection, members have the opportunity to have their prescriber change the prescription to another medication, preferably the first-line medication, or in most step-therapy programs, permit the prescriber to submit a request for coverage through a PA. The pharmacist is typically involved in step-therapy programs in the capacity of directing the member to the prescriber for the change or PA or performing this service for the member directly with the prescriber.

An opportunity exists for a step-therapy intervention for the renin-angiotensin-system (RAS)-blocking drug class consisting of first-line therapy with angiotensin-converting enzyme inhibitors (ACEIs) and second-line therapy with angiotensin II receptor blockers (ARBs). In this issue of *JMCP*, Yokoyama et al. report the first evidence in the literature of the outcomes in drug cost and therapeutic selection of step-therapy intervention for the RAS drugs. Using the standard pharmacy benefit smart-edit technology, with grandfathering, the authors found an adjusted $0.03 per member per month (PMPM) savings and an estimated unadjusted savings of $0.05. However, about 7% of members whose claim was rejected at the point of service did not have any antihypertensive medication claims during 12 months of follow-up.

The results by Yokoyama et al. have been replicated using a comparable step-therapy program implemented in 2006, which led to an unadjusted PMPM savings of $0.11. In this study, 9% of members whose claims were rejected at the point of service received no antihypertensive medication during a minimum of 4-month follow-up. The higher pharmacy savings and percentage of members without any antihypertensive medication claims during the analysis period are likely due to the shorter duration of follow-up. Step-therapy PMPM savings have been shown to be greatest in the months following implementation, and it is intuitive that the longer members are followed, the greater the likelihood they will initiate therapy. Based on the data from the RAS-blocker step-therapy studies, it is possible that some of the pharmacy savings from this managed care intervention may come at the cost of some members going without antihypertensive medication.

An important limitation for both of these studies is the absence of the medical costs and clinical outcomes assessment. Further research is needed to better understand the potential clinical outcomes and medical costs associated with step-therapy programs, especially those programs impacting use of medication for which clinical trials have documented lower rates of endpoint events such as hospitalization or death. Of special concern are high-risk members (such as those who are post-myocardial infarction or have congestive heart failure or renal insufficiency) who may go without a RAS-blocking agent, for which studies have documented a clinical outcomes benefit. Unfortunately, the current step-therapy studies lack medical claims assessment. Thus the proportion of high-risk members going without antihypertensive therapy after their step-therapy claim rejection is unknown, as are the total health care costs.

The RAS-blocking drug class step-therapy program is one of many step-therapy programs in use today (see table). Only 3 other programs have been assessed to an extent similar to the evaluation of the RAS-blocking drug class. These programs include the nonsteroidal anti-inflammatory drugs (NSAIDs) including cyclooxygenase-2 (COX-2) inhibitors, proton pump inhibitors (PPIs), and selective serotonin reuptake inhibitors (SSRIs). The reported savings ranged from zero to $0.36 PMPM with SSRIs to $0.48 with PPIs. The lack of SSRi savings in one study and the substantial savings in another may be the result, in part, of the relative availability of fluoxetine as a generic drug in the first analysis and the subsequent availability of 3 generic SSRIs at the time of the more recent study.

The prevalence of members without a medication claim in the drug class after their point-of-service claim rejection ranged from 7% with RAS-blockers to 22% with PPIs. The pharmacy benefit savings in direct drug cost occurred as anticipated due to greater use of generics and a portion of members receiving no medication. The higher rate of members with no medication claims following the step-therapy claim rejection for the PPI and NSAID drug classes is likely due to the availability of over-the-counter alternatives. For the SSRIs and RAS-blocker drug classes, the rate of no medication claims following the step-therapy claim rejection was similar, at approximately 1 in 10 members or less.

It has become clear that one outcome of step-therapy programs...
## Commentary

**TABLE 1  Common Step-Therapy Programs**

<table>
<thead>
<tr>
<th>Core Area</th>
<th>First Line</th>
<th>Second Line</th>
<th>PMPM Savings</th>
<th>No Medication After Step-Therapy Claim Rejection</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADHD</td>
<td>Generic stimulants</td>
<td>Strattera or brand stimulants</td>
<td>No published data</td>
<td>No published data</td>
</tr>
<tr>
<td>Allergy</td>
<td>Nasal steroids</td>
<td>Leukotriene modifiers</td>
<td>No published data</td>
<td>No published data</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>Generic statins</td>
<td>Brand statins</td>
<td>No published data</td>
<td>No published data</td>
</tr>
<tr>
<td>Depression</td>
<td>Generic SSRIs</td>
<td>Brand SSRIs, brand SNRIs</td>
<td>$0.00-$0.36</td>
<td>11%</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Generic PPI</td>
<td>Brand PPIs</td>
<td>$0.48</td>
<td>22%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Generic ACEIs</td>
<td>Brand ACEIs, brand ARBs</td>
<td>$0.03-$0.11</td>
<td>7%-9%</td>
</tr>
<tr>
<td>Pain</td>
<td>Generic NSAIDs</td>
<td>Brand NSAIDs, COX-2s</td>
<td>$0.29</td>
<td>15%</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>Generic gabapentin or tricyclic antidepressants</td>
<td>Lyrica or Topamax</td>
<td>No published data</td>
<td>No published data</td>
</tr>
</tbody>
</table>

ACEIs = angiotensin-converting enzyme inhibitors; ARBs = angiotensin II receptor blockers; COX-2s = cyclooxygenase-2 inhibitors; NSAIDs = nonsteroidal anti-inflammatory drugs; PMPM = per member per month; PPIs = proton pump inhibitors; SNRIs = serotonin norepinephrine reuptake inhibitors; SSRIs = selective serotonin reuptake inhibitors; TNF = tumor necrosis factor.

is that a portion of members with a claim rejection at the point of service go on to have no claims in that class of medications. The PBM industry has already begun to address this potential concern. Two methods are currently in use by some PBMs to decrease rates of the no-medication outcome. One method is to perform rapid retrospective drug utilization review (RetroDUR). The second method involves a medical and pharmacy claims integrated smart edit.

Through the rapid RetroDUR program, providers are notified of their patients who have a step-therapy claim rejection and have not yet obtained their medication. The rapid RetroDUR program works through a process of frequently querying the pharmacy claims data to identify members with a step-therapy claim rejection and no medication claim following the claim rejection. Prescribing providers are sent a letter or telephone call informing them that their patient had experienced a step-therapy edit and that the PBM had not processed any comparable medications for the patient within a set period of days. The letter outlines the process for the member to seek second-line medication coverage.

The smart-edit method to manage absence of medication in a class associated with a step-therapy intervention involves real-time integration of a member’s medical diagnosis into the point-of-service transaction. According to David Lassen, PharmD (senior director of Care Management, Prime Therapeutics LLC; February 26, 2007), this method allows members with a high-risk diagnosis to bypass the edit. Integration of the medical diagnosis can be accomplished through the review of historical medical claims International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis codes by the PBM or by the pharmacist electronically entering ICD-9-CM code(s) at the point of service. It can also be accomplished by the prescriber entering the ICD-9-CM diagnosis code(s) during the e-prescribing event. All of these processes require medical diagnosis information to be integrated in some fashion with the pharmacy electronic claims processing system.

Currently, PBMs who receive medical data are capable of performing an integrated medical and pharmacy smart edit. For example, the edit for RAS-blockers might allow members who have a medical claim for a myocardial infarction, congestive heart failure, or renal insufficiency to electronically obtain approval for second-line coverage of the ARB. Similarly, the edit for PPIs might provide approval for second-line coverage to members with Barrett’s disease or Zollinger-Ellison syndrome. The edit for statins might allow members at high cardiovascular risk to obtain the second-line therapy; and the edit for COX-2 inhibitors might allow members with a diagnosis of prior upper gastrointestinal tract bleed or familial adenomatous polyposis to receive second-line coverage. Ideally, a combination of the rapid RetroDUR and an integrated medical and pharmacy smart edit would be applied to step-therapy programs in order to reduce the rate of members going without medication.

Understanding the impact pharmacy step-therapy programs have on therapeutic selection is the first step in an ongoing assessment of the programs. It is only through assessments of PBM utilization management programs, as reported by Yokoyama et al., that the next steps can be taken to fully understand the risks and benefits. The direct pharmacy financial outcomes appear clear. Less clear are the risks. The current pharmacy-only smart-edit step-therapy program appears to result in as many as 1 in 10 members who experience claim rejection for SSRIs or RAS-blocking medication going on to have no pharmacy claims for drugs in that class. PBMs and MCOs might do better in step-therapy program development by adding medical diagnosis...
information to the smart-edit program and following up with the rapid RetroDUR prescriber notification. The next analytic step should be assessments of the impact of step-therapy programs on clinical outcomes and total medical costs, including pharmacy provider and administrative costs.

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DISCLOSURES
The author discloses that he is employed by Prime Therapeutics, LLC, a pharmacy benefits management company.

REFERENCES
Medication Therapy Management Programs: When Will the Outcomes Come Out?

The Medicare Modernization Act requires Medicare Part D prescription drug plans (PDPs) and Medicare Advantage prescription drug plans (MA-PDs) to provide medication therapy management programs (MTMPs) as part of the benefit. As defined in the Act, MTMPs are "furnished by a pharmacist [and] designed to assure . . . that covered part D drugs are appropriately used to optimize therapeutic outcomes through improved medication use, and to reduce the risk of adverse events, including adverse drug interactions." While the Act defines basic elements of the program, it also gives PDPs and MA-PDs a large degree of flexibility for the design and implementation of the MTMP. The Act also identifies the beneficiaries who should be targeted for MTMPs (those with multiple chronic conditions, taking multiple medications, and having prescription drug expenses exceeding $4,000 per year) but allows each participating plan to develop its own specific patient eligibility criteria for MTMP enrollment.

The wide variability in MTMP patient eligibility criteria and the types of services offered to enrollees was documented in a 2006 survey of 70 health insurance plans representing more than 250 PDPs and MA-PDs. All of the surveyed plans followed the $4,000 per year in prescription drug expenses criterion, but they used a variety of methods to calculate this figure. While plans relied on predictive modeling to estimate prescription drug expenses for the year, some plans required a consistent monthly expense ($300-$350 per month for the first 2-3 months of eligibility), while others required $1,000 of expenditures in the first quarter.

There were more significant differences in plan requirements for the number of chronic conditions and the number of unique medications necessary for MTMP enrollment. The number of chronic conditions required by health plans ranged from 2 to 5, with some plans limiting the count to a specified list of chronic conditions. The number of unique medications requirement brought the most variability; while most plans required between 6 and 9 chronic medications, the range among all plans was from 2 to 24 medications, and some plans did not differentiate between episodic and chronic medication use. Further, some plans did not specify a minimum number of medications or chronic conditions required, while others did not require that all 3 enrollment criteria be met for a patient to be eligible for MTMP enrollment.

Since most PDPs and MA-PDs are now approaching (or have surpassed) 1 year of MTMP operation, the time has come to begin evaluating the successes and failures of the programs. When evaluating their programs, plans should be focusing on 2 questions: (1) Has their targeting criteria correctly identified the patients who would most benefit from medication therapy management? and (2) Has the MTMP been successful in achieving whatever goals (enrollment, health outcomes, cost savings, etc.) that the plan had established for it?

It is likely that most PDPs and MA-PDs examined historical data while developing their MTMP enrollment criteria. In a previous issue of JMCP, Daniel and Malone describe the results of a study where data from the Medical Expenditure Panel Survey were used to calculate the proportion of community dwelling seniors with annual prescription drug expenditures exceeding the $4,000 threshold for MTMP targeting and to identify the patient-specific risk factors for reaching that expenditure level. The study determined that 9.2% of patients aged 65 years or older would generate $4,000 or more in annual prescription expenses and that patients meeting the $4,000 threshold averaged 10.8 unique medications and 5.2 chronic conditions per year. These findings indicate a potential redundancy in the enrollment criteria; since 90% of patients meeting the prescription expense threshold had 3 or more chronic conditions, and 85% of patients had 7 or more unique medications, it is unlikely that the chronic condition and multiple medication requirements would eliminate more than a small fraction of the patients with prescription drug expenditures exceeding $4,000. Health plans seeking to quickly identify the patient population most likely to be targeted for MTMP could use the $4,000 annual prescription drug expenditure threshold to come up with a rather reliable estimate.

The authors also identified a list of factors that predicted whether or not a patient would meet the $4,000 threshold, including age, functional status, health insurance status, specific diagnoses, and the number of chronic conditions. This list is useful, but the factors should not be considered static. For example, the marketplace entry of generic medications for depression and gastrointestinal disorders since the end of this study's data collection period may make use of these classes of medications less likely to trigger the $4,000 threshold. Any plan conducting its own work should update its analyses periodically (at least on a yearly basis) to account for changes in the health status of the population, utilization patterns, and prescription expenses. The authors also correctly noted that some of these factors (functional limitations, help required in activities of daily living) might not help a PDP or MA-PD identify potential MTMP targets since that level of information is not typically stored in a health claims database. Plans should not rely on a claims database as the only means to identify potential MTMP targets; physicians, pharmacists, and allied health professionals should all have the opportunity to assess and identify patients who would be good candidates for MTMP.

While many of the results of the analyses performed by Daniel and Malone were self-evident, the methodology and analysis were sound, and the authors should be commended for being the first to publish such an extensive analysis of the MTMP targeting criteria. They have drawn up a blueprint that plans can follow to investigate patient factors associated with meeting the prescription drug expense threshold. Plans may benefit from replicating the study using their own data from
2006 and then modifying their targeting criteria to best identify the patients who may benefit most from MTMP enrollment.

As important as the questions regarding the identification and characteristics of the targeted population are, quantifying the benefits of MTMPs is the ultimate goal. While individual plans likely spent a great deal of time and effort developing their MTMPs enrollment criteria and design, it means little if there are no solid plans to quantify their program’s impact. The Centers for Medicare & Medicaid Services (CMS) has not yet begun to require PDPs or MA-PDs to document MTMP outcomes. For MTMPs operating in 2006, CMS only required that plans self-report the number of beneficiaries who met the target criteria, participated in the program, disenrolled from the program, and declined to participate and the total prescription costs per MTMP beneficiary per month. The application process for coverage year 2007 only required plans to describe their methods for documenting and measuring the outcomes of the MTMP.

A review of plan responses to the American Pharmacists Association (APhA) survey question regarding the measurement of MTMP outcomes indicates that quite a few plans had begun to operate their MTMP without a strategic plan to evaluate the program’s effectiveness. This finding was unsettling, especially in light of the meetings convened in summer 2004 by the American Society of Health-System Pharmacists and the Academy of Managed Care Pharmacy. At these meetings, stakeholders from pharmacy benefit managers, health plans, health care organizations, and pharmacy organizations agreed that the measurement of short- and long-term outcomes was essential to ensure individual and organizational competence.

APhA convened an outcomes measures task force in order to suggest metrics that could be used by CMS and its contractors to evaluate MTMPs. Task force recommendations regarding outcomes research for medication therapy management services (MTMSs) included (a) outcomes analyses that include both short-term metrics (such as the number of prescriptions received and therapy adherence and compliance) and long-term metrics (emergency department visits, hospitalization rates); (b) use of measures to evaluate the economic impact of MTMSs, including costs of services, quality of care outcomes, cost of quality of care, and cost of quality of life improvement; (c) use of metrics to evaluate adherence to various treatment standards and guidelines (Beers list for potentially inappropriate medications, National Cholesterol Education Program guidelines for cholesterol management, etc.); (d) monitoring for therapeutic effect and the impact on disease progression and symptomatology; and (e) adverse drug event monitoring. Plans that still have not established outcomes metrics for evaluating their MTMP can review these recommendations for examples.

It is likely that the PDPs and MA-PDs that had a solid strategic plan for evaluating MTMP outcomes have completed—or are nearing the completion of—the evaluation of their 2006 MTMP experiences. While one would hope for a flurry of publications describing MTMP successes and learning experiences in the coming months, the unwillingness of some plans to publicly post their responses to APhA’s survey and the rather vague responses of others indicate that some degree of secrecy about MTMPs remains. The sharing of MTMP learning experiences among PDPs and MA-PDs has the potential to further improve patient health through improvements in medication adherence and persistence and a reduction in adverse drug events and the overuse and underuse of prescription medications. The elements of successful MTMPs can be identified and mimicked by other programs that are starting up or have struggled to improve patient health. The sharing of information can also help establish a minimum package of MTMP services that PDPs and MA-PDs will be required to offer. Establishing these important benchmarks can reduce the trial-and-error approach to MTMP services and can improve the quality of services delivered to patients.

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DISCLOSURE
Advanced Concepts Institute has received industry grant support to study medication therapy management programs.

REFERENCES
Gamma globulin is the treatment of choice for many primary immunodeficiencies (PIDs) and autoimmune diseases. Immune globulin intravenous (IGIV) products have been used for more than 25 years and are generally considered to be safe and well tolerated.

Because of differences in their manufacturing processes, IGIV products vary with respect to pH, stabilizers (such as sugars or glycine), sodium content, and osmolality/osmolarity (Table 1). The variability among products can influence tolerability, particularly in patients with preexisting risk factors and in patients receiving high doses of IGIV. Estimates of the rate of adverse events (AEs) vary considerably (~2% to 25%), depending on the patient population. Some AEs are related to particular product characteristics, and the use of certain individual IGIV products can increase the risk for AEs. However, IGIV products are typically selected for formulary inclusion based on cost and availability without consideration of product and patient characteristics that may be related to an increased risk of AEs.

In May 2006, 10 experts in the field of IGIV therapy gathered in Miami, Florida, to participate in a roundtable. Funding for the expert roundtable and travel expenses was provided by Talecris Biotherapeutics, makers of Gamunex. These experts were included on the basis of their publication history and frequent participation in meetings concerning the use of IGIV. We convened to discuss the proper use of IGIV, particularly the patient- and product-related factors that should be considered during the formulary review process for IGIV products.

Our personal experience has been that a wide disparity exists in how formulary reviews are conducted. When discussing the formulary review process at each of our institutions, we agreed that drug reviews vary from regularly scheduled meetings that consider all IGIV products to ad hoc reviews that occur only when a new product becomes available. The formulary review process is further complicated by the fact that pharmacists may not have information concerning the risk factors that should be considered when IGIV products are selected for particular patients. Focusing on the collective expert opinion of the group and without a formal literature summary, we concluded that formulary decision makers must take into account that IGIV products are not generic and that each IGIV product has unique characteristics that may affect both tolerability and the global cost of IGIV therapy. We also emphasized the importance of consistently using a particular brand of IGIV and the risks involved in frequent product changes. Finally, we concluded that a systematic method should be used to evaluate IGIV preparations based on product characteristics, patient risk factors, and infusion-related considerations.

After the Expert Panel discussion, Dr. Sorensen drafted a conclusion statement, and all panelists were polled to determine whether each panelist agreed with the statement. We offer our consensus view on the evaluation process for IGIV products and our recommendations for the inclusion of clinical outcomes data alongside traditional considerations such as product acquisition cost and availability.

Pharmacoeconomic Considerations in IGIV Product Choice

Historically, the supply of IGIV has been limited; therefore, the primary drivers for decisions on IGIV selection have been cost and availability. Pharmacoeconomic data are limited to 1 comparative study, which indicated that IGIV manufactured using a caprylate/chromatography process (IGIV-C) compared with IGIV manufactured using a solvent/detergent process (IGIV-SD) results in cost savings, primarily due to differences in the number of hospitalizations for AEs. Assuming equal pricing of both IGIV products, this multivariate analysis showed that annual mean per-participant costs were significantly lower between those receiving IGIV-C and those receiving IGIV-SD for prescription medications ($302, 95% confidence interval [CI], $598 to $-6), hospitalization ($1,454, 95% CI, $1,828 to $-1,080), and total costs ($1,304, 95% CI, $-1,867 to $-742).

The average selling price of IGIV does not accurately reflect the total cost of treating a patient with that product. Directly identifiable costs, including preparation time and infusion time (in the outpatient setting), may also have an impact on total costs, although this amount has not been determined. In addition, product tolerability is not usually considered in the total cost of a given product. The overall cost of IGIV administration may be increased in a significant number of patients by tolerability problems common to all agents, such as fever, headache, and nausea (see the Infusion Rate section for further discussion) and occasionally by serious AEs.

The formulary review process should ensure the availability of appropriate IGIV products to match patient-specific risk profiles to product-specific characteristics to reduce the risks and costs of tolerability problems and AEs.

Formulary Review Process for IGIV

Safety, effectiveness, and cost are the 3 types of information most commonly identified by formulary committees as necessary for making drug selections. To date, only 1 study has directly compared the clinical outcomes of treatment with different IGIV products. The results of that study indicated that IGIV-C had some advantages in preventing sinopulmonary infections compared with IGIV-SD. Comparative efficacy data for other IGIV products are not available.

In our experience, safety and tolerability data for different IGIV products are not reviewed in a consistent manner during the formulary review process. For example, low or no sugar content may be considered key to good tolerability by some formulary review committees, while other committees may focus on physiologic osmolality. A number of IGIV characteristics

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<table>
<thead>
<tr>
<th>Product Specifics</th>
<th>Talecris Gamunex&lt;sup&gt;2&lt;/sup&gt; Immune Globulin Intravenous (Human), 10% Caprylate/Chromatography Purified</th>
<th>Baxter Gammagard Liquid&lt;sup&gt;1&lt;/sup&gt; Immune Globulin Intravenous (Human) 10%</th>
<th>Baxter Gammagard S/D&lt;sup&gt;4&lt;/sup&gt; Immune Globulin Intravenous (Human)</th>
<th>ZLB Behring Carimune NF&lt;sup&gt;3&lt;/sup&gt; Nanofiltered Immune Globulin Intravenous (Human)</th>
<th>Grifols Flebogamma&lt;sup&gt;5&lt;/sup&gt; 5% Immune Globulin Intravenous (Human)</th>
<th>Octapharma Octagam&lt;sup&gt;7&lt;/sup&gt; 5% Immune Globulin Intravenous (Human) 5%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average selling price* per gram&lt;sup&gt;8&lt;/sup&gt; ($)</td>
<td>60.89</td>
<td>60.89</td>
<td>51.20</td>
<td>60.89</td>
<td>60.89</td>
<td>60.89</td>
</tr>
<tr>
<td>Form</td>
<td>Liquid 10%</td>
<td>Liquid 10%</td>
<td>Lyophilized</td>
<td>Lyophilized</td>
<td>Liquid 5%</td>
<td>Liquid 5%</td>
</tr>
<tr>
<td>Preparation time</td>
<td>Ready to use</td>
<td>Ready to use</td>
<td>Unknown, must be dissolved</td>
<td>Up to 20 minutes</td>
<td>Ready to use</td>
<td>Ready to use</td>
</tr>
<tr>
<td>Indications</td>
<td>PID, ITP</td>
<td>PID associated with defects in humoral immunity</td>
<td>PID, ITP, CLL, Kawasaki syndrome</td>
<td>Immune deficiency, ITP</td>
<td>PID</td>
<td>PID</td>
</tr>
<tr>
<td>Sugar content</td>
<td>No sugar</td>
<td>No added sugar</td>
<td>20 mg/mL glucose in a 5% solution</td>
<td>1.67 g sucrose per g protein</td>
<td>50 mg/mL D-sorbitol</td>
<td>100 mg/mL maltose</td>
</tr>
<tr>
<td>Sodium content</td>
<td>Trace amounts</td>
<td>No added sodium</td>
<td>Approximately 8.5 mg/mL sodium chloride</td>
<td>&lt;20 mg sodium chloride per g protein</td>
<td>&lt;3.2 mEq/L (&lt;0.02%)</td>
<td>≤30 mmol/L</td>
</tr>
<tr>
<td>TSE removal labeling</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>pH when liquid (goal 4.0-5.0)</td>
<td>4.0-4.5</td>
<td>4.6-5.1</td>
<td>6.4-7.2</td>
<td>6.4-6.8</td>
<td>5.0-6.0</td>
<td>5.1-6.0</td>
</tr>
<tr>
<td>Osmolality/ Osmolarity (goal 280-300)</td>
<td>258 mOsm/kg</td>
<td>240-300 mOsm/kg</td>
<td>636 mOsm/L (5%)</td>
<td>1250 mOsm/L (10%)</td>
<td>384 mOsm/kg (6%)†</td>
<td>708 mOsm/kg (12%)†</td>
</tr>
<tr>
<td>Maximum infusion rate (mL/kg/min)</td>
<td>0.08</td>
<td>0.083†</td>
<td>0.067† (5%)§</td>
<td>0.13† (10%)§</td>
<td>See calculations in prescribing information.</td>
<td>0.10</td>
</tr>
<tr>
<td>Tamper-evident vials</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Shelf life/storage requirements</td>
<td>36 months at refrigerated temperature 2º-8ºC (36º-46ºF), up to 6 months at 25ºC (77ºF), do not freeze</td>
<td>36 months at refrigerated temperature 2º-8ºC (36º-46ºF), up to 9 months at room temperature within first 24 months of the date of manufacture; do not freeze</td>
<td>24 months Temperature, not to exceed 25ºC (77ºF), do not freeze</td>
<td>24 months Temperature, not to exceed 30ºC (86ºF), do not freeze</td>
<td>24 months Temperature, 2º-25ºC (36º-77ºF), do not freeze</td>
<td>24 months at refrigerated temperature 2º-8ºC (36º-46ºF), up to 18 months from date of manufacture at temperatures not to exceed 25ºC (77ºF), do not freeze</td>
</tr>
<tr>
<td>Maximum recommended dose</td>
<td>PID: 300-600 mg/kg ITP: 2 g/kg divided into 2 doses of 1 g/kg on consecutive days or into 5 doses of 0.4 g/kg given on 5 consecutive days</td>
<td>PID: 300-600 mg/kg ITP: not indicated</td>
<td>PID: 300-600 mg/kg ITP: a dose of 1 g/kg is recommended</td>
<td>PID: 0.4 g/kg ITP: 0.4 g/kg on 2-5 consecutive days</td>
<td>PID: 300-600 mg/kg ITP: not indicated</td>
<td>PID: 300-600 mg/kg ITP: not indicated</td>
</tr>
<tr>
<td>Package sizes in grams</td>
<td>1, 2, 5, 5, 10, 20</td>
<td>1, 2, 5, 5, 10, 20</td>
<td>2, 5, 5, 10</td>
<td>1, 3, 6, 12</td>
<td>0.5, 2.5, 5, 10</td>
<td>1, 2, 5, 5, 10</td>
</tr>
</tbody>
</table>

† Dependent on diluent used.
‡ Converted from 8.9 mg/kg/min.
§ Converted from 4 mL/kg/h (5%), 8 mL/kg/h (10%).
CLL = chronic lymphocytic leukemia; ITP = idiopathic thrombocytopenic purpura; PID = primary immunodeficiency; S/D = solvent/detergent; TSE = transmissible spongiform encephalopathy.
that vary among products have been linked to AEs, such as the association of IGIV products stabilized with sugar and acute renal failure.\textsuperscript{15,17} Similarly, hyperosmolality may be correlated with thromboembolic events.\textsuperscript{16,25} For consistent and thorough review, all significant product characteristics that influence tolerability and the risk for AEs should be considered during the formulary review process.

Our experience has been that IGIV products differ with regard to AE risk and that the risk of AEs should be considered the driving force in the choice of a particular IGIV product. The following criteria should be considered when evaluating IGIV products (Table 1): pH, added stabilizers, osmolality/osmolarity, formulation, concentration, volume load, and infusion rate.

**IGIV Product Considerations**

**Stabilizers**

The formation of immunoglobulin (Ig) multimers may lead to aggregation, resulting in both loss of function and increased side effects; therefore, IGIV manufacturers must employ methods to prevent Ig from aggregating.\textsuperscript{26} The optimal pH to prevent aggregation of IgG is 4-4.5.\textsuperscript{27} Two brands of IGIV are supplied at pH 4-5 (Table 1).\textsuperscript{2-7} When the pH is above 5, IGIV requires stabilizing sugars such as glucose, sucrose, sorbitol, or maltose.

Patients with renal dysfunction or diabetes, as well as the elderly, may require special consideration with respect to the use of IGIV containing sugars, although absolute AEs have not been demonstrated to date.\textsuperscript{9,12,14} While the incidence (denominator) of IGIV-associated renal AEs is not known, data from the Centers for Disease Control and Prevention indicate that 90% of IGIV-associated renal AEs occurred when products stabilized with sucrose were used; the relative frequency of sucrose-stabilized IVIG use versus other IVIG products was unknown. Of patients who experienced renal AEs, 59% had 1 or more of the following risk factors: prior renal insufficiency, diabetes, or advanced age (>65 years).\textsuperscript{17}

**Osmolarity/Osmolality**

Osmolality is the concentration of osmotically active particles in a solution and is equal to the sum of the osmoles of all the solutes in a solution. Major contributors to osmolality include sodium, sugars, and other solutes (proteins such as albumin).\textsuperscript{16} Physiologic osmolality is 280-296 mOsm/kg. IGIV solutions range in osmolality from physiologic values to approximately 1250 mOsm/L (Table 1).\textsuperscript{2-7}

When infused intravenously, hyperosmolar solutions may contribute to hemodynamic changes, thus theoretically increasing the risk of infusion-related AEs.\textsuperscript{13,21,25} For example, in a study of IGIV patients at Wake Forest University Baptist Medical Center over a 4-year period, Caress et al. determined that 0.6% of patients who received IGIV (of undetermined osmolality content) experienced a stroke. The authors stated that this high rate of stroke might be because patients receiving IGIV in the hospital setting tend to have more risk factors than nonhospitalized patients.\textsuperscript{25} High osmolality may increase the risk for AEs in patients with cardiac impairment, renal dysfunction, or high risk of a thromboembolic event. High osmolality also increases the risk of AEs in the elderly and in neonates.\textsuperscript{28,29}

Lyophilized products that are reconstituted at high concentrations to decrease volume load create solutions with a higher osmolality that may cause increased serum viscosity.
which further increases the risk for thromboembolic events.\textsuperscript{9,30,31} To decrease the conjectured risk of osmolality-related AEs, we recommend using liquid IGIV products of normal physiologic osmolality or lyophilized IGIV products that are reconstituted to a volume high enough to create a preparation of physiologic osmolality in patients at risk for osmolality-related AEs. In patients at risk for volume overload, a high-concentration product, which should be infused slowly, may be appropriate.

**Formulation**

IGIV is available in both liquid and lyophilized forms. Liquid formulations are sold at a 5% or 10% fixed concentration and are ready to use. The time between the implementation of a pharmacy order and the start of the infusion is shortened by using liquid formulations instead of lyophilized products; some lyophilized products take up to 20 minutes to dissolve.\textsuperscript{3} The staff time spent preparing the lyophilized product is not reimbursed by Medicare or other insurance providers, resulting in unreimbursed costs for the pharmacy, clinic, or clinician. Lyophilized products reconstituted at higher than 5% concentrations will have higher than normal physiologic osmolality and may increase the risk of AEs (Table 1).\textsuperscript{2-7,13,21,25,30}

**Concentration and Volume Load**

The IGIV dose for a given condition and the concentration of the IGIV preparation influence both the total volume and the time of infusion. There is an inverse correlation between the concentration of an IGIV product and the length of a typical infusion. While recommended maximum infusion rates vary for different products and for each patient, in general, a more concentrated product will allow for both a lower total fluid volume and a shorter infusion time. For example, assuming the same rate of infusion, a product at a concentration of 10% will require half the infusion time of a product at a concentration of 5%. The product at 10% concentration will lead to decreased nursing and infusion room time, ultimately leading to a projected but undeterminable reduction in the overall cost of IGIV treatment, particularly in the outpatient setting.

Liquid IGIV products are ready to use at 5% (Flebogamma and Octogam) or 10% (Gamunex and Gammagard Liquid) concentration and cannot be concentrated further. Lyophilized products are also available (Gammagard S/D and Carimune NF). The practice of reconstituting lyophilized IGIV products to a concentration greater than that recommended in the package insert in order to decrease volume and reduce infusion time must be weighed against the higher risks for AEs from the resulting increase in osmolality. Rapidly delivering lyophilized IGIV at high concentrations may also result in increased serum viscosity, which is associated with thromboembolic events such as stroke in patients with preexisting vascular disease.\textsuperscript{13,32,33} Volume status must also be monitored when larger doses of IGIV are administered to elderly patients,\textsuperscript{16} debilitated patients, or neonates.\textsuperscript{16}

**Infusion Rate**

Rapid infusion rates are associated with several common mild or “rate-related” AEs that decrease tolerability. These include low-grade fever, headache, nausea, malaise, arthralgia, chest pain and tightness, rashes, hypotension, and myalgia.\textsuperscript{11,14} Maximum possible infusion rates are listed in Table 1, and range from 0.067 to 0.1 ml/kg/min. Diagnosis, treatment, and monitoring of patients experiencing these AEs increase the total cost of treatment. Therefore, adjustment of the infusion rate and the choice of product must be carefully monitored to decrease tolerability problems. If patients experience any of the side effects noted above, the providers are advised to slow the rate of infusion and/or use preinfusion medications such as diphenhydramine, acetaminophen, nonsteroidal anti-inflammatory drugs, or corticosteroids before initiating the IGIV infusion.\textsuperscript{11} Change of product may also affect the tolerability of IGIV for individual patients. Switching to a different IGIV product is recommended when the patient exhibits repeated adverse reactions to an IGIV product despite infusion rate adjustments and the use of preinfusion medications. If these events continue with all IGIV products, it may be necessary to use an alternative route of administration or discontinue treatment. An initial decrease in infusion rate is recommended when a new product is used.

**Pathogen Safety**

Because IGIVs are derived from blood, decreasing the risk of infection is of the utmost importance. To prevent transmission of blood-borne pathogens, the manufacturers of all IGIV products incorporate processes that ensure viral inactivation and removal.\textsuperscript{34} Prion contamination has also become a theoretical concern in recent years,\textsuperscript{9} and some IGIV manufacturers have incorporated prion contaminant removal measures—cloth filtration and depth filtration—into the IGIV manufacturing process.\textsuperscript{34} Two of the 6 commercially available IGIV products have been manufactured using methods with demonstrated prion removal capabilities (Table 1); however, no documented cases of prion contamination from IGIV or other blood products have been reported, regardless of manufacturing technique.\textsuperscript{2,5}

**FDA-Licensed Indications**

The various brands of IGIV are licensed for different indications, including PID (all brands), idiopathic thrombocytopenic purpura (ITP) Gammagard S/D, Gamunex, Carimune), chronic lymphocytic leukemia (Gammagard S/D), and Kawasaki syndrome (Gammagard S/D). For a full listing of U.S. Food and Drug Administration (FDA)-licensed indications for each brand of IGIV, see Table 1.

**Dose, Package Size, and Storage**

Other IGIV product choice considerations include dose, package size, and storage. The maximum recommended doses...
of IGIV for PID and ITP are similar for the different brands of IGIV, and a range of package sizes is available for most brands (Table 1). Because larger doses (1-2 g/kg) are recommended for ITP, package size and formulation may be a relevant consideration for this indication since staff may be required to pool several vials for a single dose. To be certain of package content and sterility, patients should use IGIV products packaged in tamper-evident vials whenever possible.

**Underlying Risk Factors Necessitating Specific IGIV Product Choice**

A number of underlying risk factors (Table 2), including cardiac impairment, renal dysfunction, IgA deficiency, thromboembolic risk, diabetes, vascular disease, age (neonates and the elderly), and a history of AEs, may signal caution for the use of certain IGIV products. If any of these risk factors exist, IGIV products should be carefully selected to minimize risk. While serious AEs are rare, they can occur upon first administration of IGIV, so risk factors need to be carefully assessed for all patients. Formulary committees may consider requiring a risk assessment form as part of the order for IGIV. In cases where risk factors are identified, an immunologist should be consulted when selecting an IGIV brand.

**Recommendations and Future Directions for IGIV Formulary Reviews**

To improve the formulary review process, we recommend that (1) reviews include a comprehensive evaluation of all available products, (2) reviews occur annually, and (3) immunologists and other experienced IGIV users be included as primary reviewers and decision makers in IGIV product selection.

Selection of IGIV products should be made according to patient-specific risk factors, product-specific characteristics, and practical considerations such as cost and convenience. We recommend using a risk assessment form to evaluate each patient regardless of infusion setting. This form, to be reviewed by both the physician and the pharmacist, should help decide whether IGIV use is appropriate for the patient and which IGIV preparation to select on the basis of particular risk factors (Table 2). Ideally, the risk assessment form would be computerized to facilitate the exchange of information between physician and pharmacist. Infusion- and dose-related AEs are also important considerations, as are practical concerns such as ease of use (e.g., storage requirements, time required for product preparation before administration), ease of administration (solution concentration), and duration of infusion.

The IGIV formulary determination process must ensure that at least 1 of the brands selected for formulary inclusion is able to minimize AE-related risks in patients and provide clinicians with appropriate IGIV brand choices. This will allow clinicians and pharmacists to select appropriate IGIV products based on patient-specific risk factors.

Future initiatives to improve the formulary selection process should include more complete recording, coding, and reporting of AEs, which will result in a more informative picture of the specific AEs associated with particular IGIV products. We also call for prospective studies to evaluate clinical and pharmacoeconomic outcomes for all individual brand IGIV products.

**Conclusions**

IGIV formulary decision makers should select an adequate number of IGIV brands with different product characteristics for formulary inclusion to enable clinicians and pharmacists to match IGIV products to specific patients based on patient-risk profiles. The panel participants concur that at least 2 brands should be included, and some authors feel that up to 4 brands are necessary.

Individual IGIV brands have distinctly different characteristics. Products differ in their preparation and infusion times. These differences may affect the cost of administration and the risk of AEs that may be associated with their use, although neither the relative administrative costs nor the risk of AEs has been quantified. Patients vary in their responses to different products; therefore, each patient must be individually matched with the most appropriate IGIV product by the physician and pharmacist. Prudent, specific IGIV product selection that compares patient tolerability and risk profiles will result in better tolerability and lower risk for AEs, improving patient outcomes. Better IGIV infusion experiences together with more practical dosing and infusion rates may produce better patient outcomes and reduce overall costs associated with IGIV therapy.

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Outcomes of Sword Swallowing 
and Pharmaceutical Step-Therapy Interventions

Witcombe and Meyer found that sword swallowers experience side effects. While this outcome is perhaps not surprising, outcomes research was necessary to determine if there were factors related to the side effects. The research showed that esophageal tears were more likely when the swallow was (a) distracted or (b) swallowed an unfamiliar sword.

Like sword swallowing, step-therapy interventions that require prior use of a lower-cost therapy with effectiveness that is equivalent to a higher-cost therapy would, on their face, appear to have certain self-evident outcomes. However, research is necessary to answer questions such as the magnitude and durability of drug cost savings and whether drug cost savings are offset or overwhelmed by undesirable service outcomes or administrative costs. In an article published in JMCP in mid-2006, Dunn et al. showed that the cost per day for all antidepressant drug therapy was reduced by 9% as the result of a step-therapy intervention that required use of a generic selective serotonin reuptake inhibitor (SSRI) prior to coverage of a brand-name antidepressant, producing pharmacy benefit savings of $0.36 per member per month (PMPM) in 2005 dollars.

In the current issue of JMCP, Yokoyama et al. found that a step-therapy intervention that required use of an angiotensin-converting enzyme inhibitor (ACEI) prior to coverage of an angiotensin II receptor blocker (ARB), saved 13% in direct drug cost for all antihypertensives versus the comparison group without the ARB step-therapy intervention. The authors estimated that drug cost savings were $0.03 PMPM across the population of approximately 1 million members. However, while this $0.03 PMPM estimated savings was calculated over 12 months of follow-up, the identification period was only 6 months. Additionally, the study population was limited to continuously enrolled members, who represented only 76% of patients fulfilling all other study criteria. Therefore, actual drug cost savings may be $0.06 PMPM or more if extended to a full 12 months of ARB step-therapy intervention and to both continuously and noncontinuously enrolled members.

For a managed care organization population of 1 million members, the annual savings in drug costs from this ARB step-therapy intervention is at least $360,000 or as much as $720,000, in 2002-2003 dollars. While these cost savings are impressive, the authors acknowledge that potentially offsetting costs in the administrative time required in physician offices and pharmacies were not assessed, and a return on investment could not be calculated because the administrative costs incurred by the pharmacy benefits manager in administering the intervention were not measured.

While the direct drug cost savings of $0.06 PMPM or more from the ARB step-therapy intervention may be offset somewhat by administrative or provider personnel costs, the drug cost savings may be underestimated by Yokoyama for another reason. The absolute rates of initiation of either ACEI or ARB therapy were 2.4 times higher in the comparison group versus the intervention group, 2.2% of approximately 2 million members in the comparison group versus 0.9% in the intervention group. After application of the selection criterion of at least 15 months of continuous eligibility, the 2.4 times higher rate of initiation of either an ACEI or ARB remained the same in the comparison group (1.7%) versus the intervention group (0.7%). We don’t know the reason(s) for this difference, but there are at least 3 plausible contributing factors. The comparison group was both older (mean 57.6 years vs. 52.9 years, P<0.001) and had a higher Chronic Disease Score (mean 1,860.95 vs. 1,598.30, P<0.001). A third possible explanation is a “sentinel effect” in which prescribers avoid the target of the intervention and select alternative drug therapy.

Some might lump the sentinel effect with the “hassle factor” for providers in managed care. Yet, research on the rigor of step therapy suggests that not only is the cost of the hassle factor overwhelmed by cost savings in the target therapy but the step therapy intervention can also produce favorable clinical outcomes. Population-based observational research reported by Mamdani et al., for the period from January 1996 to November 2002, showed that a restrictive, step-therapy intervention in British Columbia that placed cyclooxygenase 2 (COX-2) inhibitors as fourth-line therapy after at least 3 non-steroidal anti-inflammatory drugs (NSAIDs) was associated with a 25% increase in prevalence of use of NSAIDs, including COX-2 inhibitors (from 8.7% to 10.9%) in persons aged 66 years or older. In Ontario, where step therapy was also recommended, the intervention was not as restrictive as in British Columbia, where “special authority approval” was required for use of a COX-2 inhibitor, and there was a larger, 51% increase in the prevalence of use of NSAIDs (from 10.9% to 16.5%). Putting aside the clinical and cost outcomes of adverse cardiovascular events associated with the use of COX-2 inhibitors, the rate of hospital admissions due to gastrointestinal (GI) hemorrhage increased significantly in Ontario, by about 16%, or a rate of 2 admissions per 10,000 older adults above the expected value (P<0.01). There was no increase in hospital admissions per 10,000 older adults in British Columbia, with its more restrictive step-therapy intervention for COX-2 inhibitors, a lower overall absolute rate of use of all NSAIDs, and lower rate of increase in the use of all NSAIDs following the market introduction of the COX-2 drugs.

The opportunity for cost savings from step therapy for COX-2 inhibitors was identified 4 years ago when Cox et al. showed that 65% of patients new to COX-2 therapy did not have an indicated risk for GI hemorrhage, 68% did not have evidence of prior use of first-line therapy with another NSAID, and a combined 45% of new users of COX-2 inhibitors did not have either a possible indication of GI risk or prior use of first-line therapy. Subsequent research showed that the cost savings were $0.29 PMPM in 2002-2003 dollars in a 20,000-member pharmacy benefit plan with...
step-therapy intervention for COX-2 inhibitors.  

In this issue of JMCP, Gleason compares some of the cost savings reported by step-therapy interventions and outlines the opportunities for which we do not yet have results from outcomes research, including step therapy for cholesterol management, allergy, and attention-deficit/hyperactivity disorder. The present article by Yokoyama et al. is the first peer-reviewed, published report of the cost and utilization outcomes associated with an ARB step-therapy intervention. However, Gleason et al. reported recently in a poster abstract the results of an ARB step-therapy intervention that reduced the direct drug cost for antihypertensive drug therapy by $0.11 PMPM in the first 4 months of follow-up across an entire health plan of 65,524 members. The larger savings reported by Gleason et al. may be attributable, to the lack of a control group as well as to the nature of the intervention. In both the Yokoyama et al. and Gleason et al. interventions, the health plans required a trial of an ACEI or a prior-authorization request before permitting coverage of an ARB. In Gleason et al., the step-therapy program was more stringent: only generic ACEIs were considered first-line therapy, and the health plan required a generic ACEI trial or a prior-authorization request submitted by fax before a brand ACEI or ARB was covered.

The magnitude of the effect on cost outcomes associated with step therapy would appear to be proportional to the restrictiveness of the intervention. The difference in magnitude of cost savings in the ARB step-therapy interventions described by Gleason et al. versus Yokoyama et al. and the magnitude of difference in the increase in NSAID use and hospitalization outcomes reported by Mamdani et al. associated with the more restrictive COX-2 step therapy in British Columbia versus Ontario support this hypothesis. In Ontario, the “Limited Use” system requires the prescriber to merely write a code number (“316” for osteoarthritis or “317” for rheumatoid arthritis) on the prescription to permit coverage and payment for a COX-2 inhibitor, signifying that the patient has failed an adequate trial of acetaminophen (e.g., acetaminophen 1 gram 4 times daily for several weeks) and has had a history of a documented, clinically significant ulcer or GI bleed or failure or intolerance with at least 3 listed NSAIDs. In British Columbia, coverage of a COX-2 inhibitor requires prior use of at least 3 listed NSAIDs or submission of a prior-authorization request through a paper-based system. These observations should remind us that not all step-therapy interventions are “created equal,” and it is important to qualify step-therapy interventions when investigating clinical, service, and cost outcomes and when reporting the results of these investigations. Perhaps it is time to propose a categorical system to rate step-therapy interventions by the degree of restrictiveness. There are at least 2 dimensions of step-therapy restrictiveness: (a) the medium-process itself (e.g., hand-written code number, automated voice response, or FAX submission form), and (b) the specificity of the exception criteria (e.g., signature of the physician vs. open-ended request for clinical justification). This categorical system for rating restrictiveness may be helpful in interpreting the results of these population-level evaluations of step-therapy interventions.

The timing of these first reports in the literature by Yokoyama et al. and Gleason et al. (as a poster abstract) on the cost and utilization outcomes of ARB step-therapy interventions coincides with a recent report on the comparative effectiveness of ACEIs and ARBs in treating hypertension as determined by the Effective Health Care Program of the Agency for Health Research and Quality in January 2007. This AHRQ report sought to determine if ACEIs and ARBs are effectively equivalent in treating hypertension as assumed by most clinicians by evaluating the literature on intermediate outcomes (e.g., blood pressure control, rate of use of a single hypertensive agent [monotherapy]), and endpoint outcomes, including all-cause mortality and cardiovascular disease-specific mortality. In addition to comparative therapeutic effectiveness, AHRQ sought answers to the question of comparative safety outcomes (e.g., withdrawal from therapy due to adverse events) and the incidence of adverse events such as angioedema, cough, weight gain, and impaired renal function. The evidence showed no advantage of ARBs over ACEIs in intermediate outcomes (e.g., blood pressure control, effect on lipid values, left ventricular mass index, or ejection fraction) or in endpoint outcomes (e.g., all-cause mortality, disease-specific mortality, quality of life, or cardiac events such as myocardial infarction [MI]). The ARBs were found to have a lower risk of cough compared with ACEIs, pooled odds ratio 0.341, representing a difference of 5.7 percentage points based on clinical trials, which specifically query subjects regarding symptoms, but a difference of only 1.3 percentage points for cohort studies. Thus, the AHRQ report points out, the numbers of patients needed to treat with ARBs to prevent 1 patient with cough are 18 based on the clinical trial data or 76 using cohort data. The latter number would have more clinical relevance.

The AHRQ report on comparative effectiveness also found no reliable difference between ACEIs and ARBs in the intermediate outcomes of persistence and adherence. In the translation of outcomes from randomized controlled trials (RCTs) to the real world, in which drug therapy is discontinued for many reasons, including adverse events or perceived ineffectiveness, assessment of medication adherences helps provide the glue to connect RCTs with population health. In research not considered in the AHRQ report of comparative effectiveness, Shrank et al. found, in their examination of 6 drug classes including ARBs and ACEIs, that adherence with therapy was 6.6% greater for patients prescribed generic drugs versus nonpreferred (nonformulary) brand drugs (P<0.001). Adequate adherence was also more common for generic drugs compared with nonpreferred drugs (odds ratio [OR]: 1.62, 95% confidence interval [CI], 1.39-1.89. Out-of-pocket cost
may be an important factor in these findings since generic drugs have the lowest out-of-pocket cost (member copayment). A mail survey of nearly 18,000 adult senior respondents found that about 25% reported not taking prescribed medication due to cost. Fortunately for health plans and for patients, all of the ACEIs except ramipril are available by generic name and most, including the former blockbusters enalapril (Vasotec), lisinopril (Zestril), and benazepril (Lotensin), are available at a total cost before member cost share of less than $0.60 per day of therapy. And for ramipril, recent evidence appears to close the book on any remaining questions regarding a class effect of the ACEIs on endpoint outcomes; Tu et al. found no difference in the combined endpoint of death or hospital readmission for acute myocardial infarction (AMI) in a 2-year follow-up of AMI patients who used ramipril versus enalapril (adjusted hazard ratio [HR], 0.95; 95% CI, 0.79-1.15), vs. lisinopril (HR, 1.02; 95% CI, 0.84-1.25), or compared with other ACEIs (HR, 1.08; 95% CI, 0.88-1.32). Finally, it is not yet clear that ARBs are as safe and effective as ACEIs in long-term use, as noted in the AHRQ report on comparative effectiveness. Publication of the results of the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial in 2004 raised concern about the possible relative risk of ARBs, particularly in patients at high risk of cardiovascular events. An outcome of the VALUE trial that was not cited in the abstract was that the ARB valsartan produced a statistically significant 19% relative increase in the prespecified secondary endpoint of MI (fatal and nonfatal) compared with amlodipine. Verma and Strauss in an editorial in the British Medical Journal posited that (a) the results of the VALUE trial should be acknowledged in the context that ARBs may increase the risk of MI and (b) perhaps it is time to consider informing patients of this apparent increased risk. However, McDonald et al. in a subsequent systematic review concluded that there was not an increased risk of MI compared with placebo (OR, 0.94; 95% CI, 0.75-1.16) or compared with ACEIs (OR, 1.01; 95% CI, 0.87-1.16).

There is much that we do not know. Outcomes research is necessary whether the intervention is sword swallowing or step therapy to manage population health care. In the present article by Yokoyama et al., the drug cost savings appear to be underestimated, but the potential costs in patient or provider dissatisfaction and the personnel costs incurred in pharmacy and physician offices were not assessed. Thus far, the evidence shows that step-therapy interventions can help steer patients to the therapy with the greatest value.

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Pharmacoeconomic Modeling of Drug Therapies for Multiple Sclerosis—are We Building Houses on Sand?

Multiple sclerosis (MS) is a disabling neurological disease that attacks primarily young adults and affects more than 350,000 in the United States and 2 million worldwide. There is no cure for MS and no therapy completely halts progression of the disease. The report from the Committee on Multiple Sclerosis of the Institute of Medicine (2004) concluded that the principal need in the management of MS is more research and noted in Recommendation no. 11 that many of the pivotal clinical trials of MS disease-modifying therapies were terminated early, resulting in the loss of potentially valuable clinical data that might be used to guide other research.

Fortunately, many MS patients do well with no drug therapy at all since the drug therapies currently approved by the U.S. Food and Drug Administration (FDA) for use in MS have significant side effects. The 6 drugs approved by the FDA include 5 immunomodulators and 1 antineoplastic agent with immunosuppressant properties (see Table). Prior to the introduction of these drugs, the first in 1993, steroids were used to reduce the duration and severity of attacks in some patients. The second category of drug treatment for MS included muscle relaxants and tranquilizers such as baclofen, tizanidine, diazepam, clonazepam, and dantrolene to help manage the spasticity that can occur as either sustained or intermittent stiffness.

Khan et al. in 2002 raised the obvious question about the relative value of the 4 immunomodulator therapies for relapsing-remitting multiple sclerosis (RRMS) available at that time and suggested that subcutaneous glatiramer acetate (SC GA, Copaxone), interferon β-1b (SC IFNβ-1b, Betaseron), and the SC dose form of IFNβ-1a (Rebif) may be more effective than the intramuscular (IM) dose form of IFNβ-1a (Avonex). This conclusion was based, in part, on the results of 2 comparative trials of high-dose interferon (250 mcg SC IFNβ-1b or 44 mcg SC IFNβ-1a every other day) versus low-dose interferon (30 mcg IM IFNβ-1a once weekly). The results of these 2 comparative trials, (INCOMIN [INdependent COMparison of INterferons] and EVIDENCE [EVIidence of Interferon Dose-response: European North American Comparative Efficacy]) support the greater efficacy of the higher dose and/or more frequent administration of interferon for treating RRMS in patients with stable disease (i.e., without evidence of clinical or disease activity as determined by magnetic resonance imaging [MRI]).

In this issue of JMCP, Bell et al. do a masterful job of building and exercising a pharmacoeconomic (PE) model to estimate the cost-effectiveness of treatment of RRMS with 4 of the currently available immunomodulating therapies. Unfortunately, the foundation for this construction has significant cracks. Foremost among the limitations is the absence of evidence to support some of the assumptions in the model. This is not the fault of the authors of the pharmacoeconomic model but a shortcoming of all of the randomized clinical trials of these drugs. Rice et al. in their Cochrane Database Systematic Review (2001) found a high dropout rate; only 76% (N=919) of 1,215 patients in 7 randomized controlled trials (RCTs) contributed to the final study results, which included benefits in RRMS exacerbations (relative risk [RR], 0.80; 95% confidence interval [CI], 0.73-0.88; \( P < 0.001 \)) and progression of the disease at 2 years follow-up (RR, 0.69; 95% CI, 0.55-0.87; \( P = 0.002 \)).

The conundrum in these findings regarding interferon therapy for MS is the “methodological inadequacies.” In the worst case scenario that assumes all dropout patients progressed in their disease, the inclusion of the missing data would eliminate the treatment effect (RR, 1.31; 95% CI, 0.60-2.89; \( P = 0.50 \)).

The list of the methodological shortcomings in the clinical trials of the interferon therapies for MS includes inadequate allocation concealment, incomplete reporting of proportion of treatment dropouts, as well as failure to calculate treatment effects in intent-to-treat analyses. In addition, due to the “prominent” side effects associated with these treatments, it is appropriate to evaluate the results as if single-blind rather than double-blind trials as they are described in the medical literature and defined in Table 1 of the article by Bell et al. Added to this list of 4 “methodological inadequacies” are 2 more characteristics that render assessment of the clinical value of these drugs an exercise in frustration, if not futility—the common failure to report treatment side effects and adverse events after 2 years of follow-up and no information regarding the impact of treatment, including side effects, on the quality of life of patients.

Bell et al. also rely on some squishy evidence on lost worker productivity for persons with MS. For example, in Lage et al., patient records were identified with at least 1 medical claim with a diagnosis of MS (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] code 340.xx) from 2000 to 2002. Of the 284 patient records in the administrative claims database that met this criterion and had at least 18 months continuous eligibility, 166 (58.5%) did not receive any of the 3 immunomodulator drugs available at the time, and only 16 patients had at least 1 claim for IFNβ-1b, 28 patients for SC GA, and 74 patients for IM IFNβ-1a. More important, than the small patient counts for each of the 3 immunomodulators, the total days of time away from work in the human resources database includes workers’ compensation as well as short-term disability, and absenteeism includes vacation time combined with sick days. Hence, the “productivity costs” estimated by Bell et al. from the “lost work time” reported by Lage et al. may have little or nothing to do with MS.

Finally, Bell et al. assigned value to the incidence of neutralizing antibodies (NAbs), which may inhibit the efficacy of β-interferon, specifically a NAb incidence of 2.2% for IM IFNβ-1a, 17.4% for SC IFNβ-1a, and 36.4% for SC IFNβ-1b, thereby tilting the advantage to GA. However, the most recent results from the INCOMIN Trial Study Group
### Table: Disease-Modifying Drugs Approved in the United States for Multiple Sclerosis (MS)

<table>
<thead>
<tr>
<th>Generic Drug Name (Abbreviation) [Brand Name]</th>
<th>Date of FDA Approval (Drug Class) [Dose]</th>
<th>FDA-Approved Indication for Multiple Sclerosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>SC interferon beta-1b (SC IFNβ-1b) [Betaseron]</td>
<td>July 23, 1993 (immunomodulator) [SC 250 mcg QOD]</td>
<td>For relapsing forms of MS to reduce the frequency of clinical exacerbations.</td>
</tr>
<tr>
<td>IM interferon beta-1a (IM IFNβ-1a) [Rebif]</td>
<td>May 17, 1996 (immunomodulator) [IM 30 mcg weekly]</td>
<td>For relapsing forms of MS to slow the accumulation of physical disability and decrease the frequency of clinical exacerbations. Patients with routine MS in whom efficacy has been demonstrated include patients who have experienced a first clinical episode and have MRI features consistent with MS. Safety and efficacy in patients with chronic progressive MS have not been established.</td>
</tr>
<tr>
<td>SC glatiramer acetate (SC GA) [Copaxone]</td>
<td>December 20, 1996 (immunomodulator) [SC 20 mg daily]</td>
<td>For reduction in the frequency of relapses in patients with RRMS.</td>
</tr>
<tr>
<td>Mitoxantrone [Novantrone]</td>
<td>October 13, 2000 (antineoplastic agent) [IV 12 mg/m² Q3M]</td>
<td>For reducing neurologic disability and/or the frequency of clinical relapses in patients with secondary (chronic) progressive, progressive relapsing, or worsening relapsing-remitting MS (i.e., patients whose neurologic status is significantly abnormal between relapses). Mitoxantrone is not indicated in the treatment of patients with primary progressive MS.</td>
</tr>
<tr>
<td>SC interferon beta-1a (SC IFNβ-1a) [Reblif]</td>
<td>March 7, 2002 (immunomodulator) [SC 8.8, 22, or 44 mcg TIW]</td>
<td>For relapsing forms of MS to decrease the frequency of clinical exacerbations and delay the accumulation of physical disability. Efficacy in chronic progressive MS has not been established.</td>
</tr>
<tr>
<td>Natalizumab [Tysabri]</td>
<td>November 23, 2004 (immunomodulator) [IV 300 mg Q4W]</td>
<td>For relapsing forms of MS to reduce the frequency of clinical exacerbations. The safety and efficacy of natalizumab beyond 1 year of therapy are unknown, and the safety and efficacy in chronic progressive MS have not been established.</td>
</tr>
</tbody>
</table>

* Data for this table derived from Facts and Comparisons 4.0, February 2007 and drugs@FDA.
† Originally approved by the FDA on December 23, 1987, for chemotherapy indications.
‡ Marketing of natalizumab was voluntarily suspended by the manufacturer in 2005 because of several reports of significant adverse events. In 2006, the FDA reapproved sale of the drug for MS but under strict treatment guidelines involving infusion centers where patients can be monitored by specially trained physicians.
FDA = U.S. Food and Drug Administration; IM = intramuscular; IV = intravenous; MRI = magnetic resonance imaging; Q3M = every 3 months; Q4W = every 4 weeks; QOD = every other day; RRMS = relapsing-remitting multiple sclerosis; SC = subcutaneous; TIW = 3 times per week.

(2006) showed that NAb status did not affect the risk of MRI activity for every-other-day dosing of β-interferon versus less frequent dosing, and research is ongoing regarding the importance of NAB titers in the decline of patient response to IFNβ.

In February 2002, the National Institute for Clinical Evidence (NICE) released its Technology Appraisal Guidance No. 32, Beta interferon and glatiramer acetate for the treatment of multiple sclerosis, in which none of the 4 immunomodulator therapies were recommended for use in treating MS. NICE researchers determined that the 4 drugs were not cost effective, citing a cost of up to $3 million per quality-adjusted life-year (QALY) in 1 study. The NICE evaluation cited the sensitivity in the economic model to assumptions such as the effect of relapse on quality of life and the time horizon for projection of therapeutic benefit. NICE determined that there was insufficient evidence to support the assumption that a treatment benefit occurs long term after the cessation of treatment. Making this adjustment increased the cost per QALY from the range of $70,000 to $208,000 (using a 2-to-1 conversion from English pounds to U.S. dollars) at 20 years to the range of $240,000 to $678,000 when treatment stops at 10 years.

Another punishing blow for the immunomodulators came 2 years after the Cochrane Systematic Review when the same authors provided additional examination of the 7 RCTs for the interferons published between 1993 and 2002. They concluded that the proportion of dropouts between 1 year and 2 years of follow-up removed the therapeutic effects of the interferons in sensitivity analyses for exacerbations, RR, 1.11 (95% CI, 0.73-1.68) and RR, 1.31 (95% CI, 0.606-2.89) for disease progression. In other words, the interferons had no effect at 2-years follow-up on either MS exacerbations or MS disease progression when the dropouts from the clinical trials were considered and the results were evaluated on the basis of intent to treat. In addition, none of the 7 RCTs reported quality-of-life outcomes, including the impact of side effects.

Interviews with MS patients who have discontinued therapy with injectable interferons or SC GA provide additional insight into the low likelihood of long-term treatment with these drugs and the reasons for discontinuation. Daugherty et al. interviewed 108 MS patients prescribed IM IFNβ-1a, SC GA, or SC IFNβ-1b by physicians in a university-based...
neurology clinic. The rate of discontinuation ranged from 28% to 41% (28% of patients prescribed SC GA, 34% for IM IFNβ-1a, and 41% for SC IFNβ-1b). The 4 principal reasons for discontinuation were adverse effects (52%), physician-documented disease progression (40%), patient perception of ineffectiveness (20%), and cost (4%).

All of this loose sand makes a poor foundation on which to build a sophisticated PE model. This work by Bell et al., while some of the most sophisticated PE work to date in this area of immunomodulator therapy (aside from the NICE analysis), reminds us of the influence of assumptions in the use of economic models. Second, the present exercise underscores the high economic cost per desired outcome in MS. Clearly, new therapeutic options are needed for this disease that affects more than 1 in 1,000 in the United States and for which there is no drug therapy proven to be effective at reducing the frequency of relapses or slowing progression of the disease for more than 1 year.

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REFERENCES
Correction Necessary Regarding CMS Guidance for Coverage of New Multiple-Source Brand Drugs

To the Editor:
In their article, “Medicare Part D: Selected Issues for Pharmacists and Beneficiaries in 2007,” Kilian and Stubbings state that, if a plan replaces a brand medication with its generic equivalent, the plan must continue to cover the brand for affected enrollees at the original copay for the remainder of the year. I do not believe this to be an accurate interpretation of the Centers for Medicare & Medicaid Services guidance.

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DISCLOSURE
The author discloses no potential bias or conflict of interest relating to this letter.

REFERENCE

The Authors Respond:
DePue is correct. Part D plans may make maintenance changes to their formulary, such as replacing brand-name with new generic drugs or modifying formularies as a result of new information on drug safety or effectiveness. Those changes must be made in accordance with the approval procedures described by Block and following 60 days notice to the Centers for Medicare & Medicaid Services (CMS), state pharmacy assistance programs, prescribers, network pharmacies, pharmacists, and “affected enrollees.” There are other types of formulary changes that are not considered maintenance changes, such as changing preferred or nonpreferred formulary drugs, adding utilization management, removing dosage forms, increasing cost sharing on preferred drugs (unrelated to the reasons stated above), or exchanging therapeutic alternatives (either by formulary addition/removal or tier exchanges). For these additional types of formulary changes approved by CMS, Part D plans should make such formulary changes only if enrollees currently taking the affected drug are exempt from the formulary change for the remainder of the plan year.

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Manufacturer Response to AMCP Format Dossier Requests

To the Editor:
We applaud Spooner et al.’s report on requests for an AMCP Format-based dossier and submissions by pharmaceutical manufacturers. Case study reports by individual plans provide a context for understanding the diffusion of the Format’s use. Although secondary to the study’s main focus, their comments on a possible relationship between formulary placement and dossier submission raise a critical issue in a voluntary process such as this—will manufacturers see their interests better served by voluntarily submitting a dossier or is opting out without a downside risk?

A formulary placement decision is the result of numerous considerations, such as the clinical need for the product under review; the existence of viable alternatives; safety profiles; all else being equal, the relative costs for alternative products; and the evidence and analysis provided by a credible dossier. The number of variables for which data would be needed and the sample size for the number of organizations and product decisions that would provide adequate statistical power for stable estimates of effect for each of these factors require an effort that is unlikely to be logistically feasible for both methodological and business reasons.

Disentangling the effect of the dossier alone or attributing a decision about a product’s placement to the existence of a dossier might be impossible quantitatively, but inferences can be generated qualitatively. Unfortunately the Spooner et al. study was not designed nor was it able to evaluate decisions qualitatively. It is interesting, however, that their observed preferred formulary placement (16.1%) is close to the reported percentage of innovative products approved in the National Institute for Health Care Management Foundation (15%). This comparability does not prove that these decisions were based on an innovation scale, but it does reinforce the dossier’s role—to identify evidence needed, to define how it should be presented, and to provide more complete data for a sound Pharmacy & Therapeutics (P&T) committee decision. Its role is not to be an evaluation process to lower prescription drug costs, a sales or marketing tool, a formulary kit, or a simple pharmacoeconomic evaluation tool.
Colmenero observed a significant association between dossier quality and whether the drug is an innovative product. We intuitively expect this since manufacturers of products that represent a clinically significant advance in therapy would logically embrace the AMCP Format as a vehicle to showcase these products’ therapeutic value. If the payer does not require a dossier as a precondition for formulary review, this factor could be an important confounder.

Unlike the experience in some other nations, the provision of a dossier using the suggested AMCP Format is voluntary, not part of a regulatory process. The Format was created to meet the information needs of P&T committees when they make decisions about product placement on a formulary. Success through a voluntary approach and arising from the marketplace may avoid a regulatory approach to obtaining the information contained in a dossier, and it is more consistent with an American preference. There is a long, slow learning curve for the development and integration of clinical and economic information into a meaningful dossier—Australia’s experience suggests that regulation, explicit procedures for compilation, and fiscal consequences do not assure content or quality of the information and economic pharmacoeconomic models.

The Format provides an opportunity for improved communications between manufacturers, health plans, and pharmacy benefit managers (“Communication—The Key To Success”). The Format recommends that this communication begin about 6 months prior to the launch of a product—enough time for discussions rather than demands regarding data needs and other aspects of the dossier request. Spooner et al’s methodology used telephone and e-mail requests “about 8 weeks before the committee meeting.” It is likely that this design decision had an impact on the observed results since only products for which a dossier was already available would have met this request.

From an industry point of view, not responding to an unsolicited request for a dossier is a lost opportunity. In the absence of the dossier process, the only information industry can legally provide is the information contained in the U.S. Food and Drug Administration-approved label. If the industry wants to communicate information that is not in the label (e.g., other supportive clinical studies, budget impact analyses, database studies, etc.), then the dossier process, in response to an unsolicited request, is the only mechanism that will allow them to do it.

We encourage more assessments of the use of the AMCP Format and study designs that make clear inferences about the relationship between the dossier and the subsequent formulary decision. Spooner et al. does not do this, but that was not their purpose. Our goal remains as stated in the introduction to the dossier: “The AMCP Format has the potential to serve as a national, unifying template for P&T committees to consider clinical and economic information in a systematic and rigorous fashion. It is a welcome development for a U.S. health system that is in need of more rigorous evaluation of evidence.”

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DISCLOSURES
Alan Lyles and John D. Watkins are members of the AMCP Format Executive Committee. Lyles has consulted with pharmaceutical companies, PBMs, health plans, and governments.

REFERENCES

The Authors Respond:
We do not dispute Lyles and Watkins’ suggestion that the results of the analysis may have been different with a longer lead time in making unsolicited requests for dossiers. As envisioned in the AMCP Format, health plans or pharmacy benefit managers who are able to set their Pharmacy & Therapeutics committee agenda 6 months or more in advance may have the opportunity to collaborate with manufacturers to build dossiers with customized content, particularly with regard to economic and disease state modeling. However, our experience in having only 2 months lead time to prepare materials for P&T committee evaluation may more closely approximate the real-world conditions that many health plans face. Further, no manufacturer has offered us the opportunity to collaborate with them to build a customized dossier as a precondition for formulary review, this factor could be an important confounder.
dossier. In this instance, the short lead time and the inability to disclose the identity of the health plan we were working with were clear—and likely insurmountable—barriers to developing a customized dossier. However, dossier requests for other clients, with longer lead times and the ability to share plan-specific data, have met the same fate. Our experiences suggest that giving longer notice to manufacturers does not increase the likelihood of collaboration between the parties to build a customized dossier.

We thank Lyles and Watkins for their interest in our research. We share their goal, and the goal of the AMCP Format Executive Committee, to bring more and better evidence to members of P&T committees to better inform formulary decision making.

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January 2007 Supplement Correction
Solomon DH. The comparative safety and effectiveness of TNF-α antagonists in adult rheumatoid arthritis study by the AHRQ Effective Health Care Program. J Manag Care Pharm. 2007;13(1)(suppl):S7-S18.

The revised title is “The Comparative Safety and Effectiveness of TNF-α Antagonists.”

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