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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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REFERENCE

Rolf Hicker chose the northern part of the Brooks Range in Alaska for the setting of his Igloo With Dancing Northern Lights photograph. In addition to the beautiful colors in this picture, Hicker’s artistic composition adds to its appeal. The viewer’s eye is drawn from the northern lights on the top left, across the mountain range and field of snow toward the igloo on the bottom right of the photo. “I built the igloo over a period of three days. In order to build it, I had to find the right kind of snow to work with, and then Compact it. I sawed the compacted snow into ice bricks and constructed the igloo,” says Hicker. “Then the waiting game began! After two weeks of enduring frigid temperatures that got down to -45º Celsius [-49º Fahrenheit], the northern lights were finally positioned just right. It happened on a crystal-clear night—I had to work quickly to capture the moment when the dancing veils of light became active.” The result is a portrait of a frozen landscape that is nothing less than “brrr-illiant.”

Most people are familiar with the term “aurora borealis” (northern lights), found in the Northern Hemisphere, but the same phenomenon, called aurora australis, also occurs in the Southern Hemisphere. Auroral displays are created when protons and electrons are shot from the sun, striking the earth’s upper atmosphere. When these highly charged particles reach the earth’s magnetic field, some get trapped and move toward the northern and southern magnetic poles. As the particles collide with atoms and molecules in the atmosphere, energy is released. Some of this energy emerges in the form of glowing auroras. Most auroras occur about 70 miles above the earth, and appear as arcs, clouds, and streaks that can move, brighten, or flicker suddenly. Green is the most common color in an aurora, but many colors can be seen or filmed before.

Hicker has a degree in business management and produced films and slide shows in Germany for more than 18 years. He also specializes in Web solutions and marketing for photography- and travel-related Web sites. His own Web site, www.hickerphoto.com, showcases his stunning photographs and provides links to international travel and tour sites. Many of Hicker’s photos are available as stock images, and his work is represented by numerous stock photo agencies.

Traveling around the world taking photographs in remote locations, Hicker captures dramatic impressions of nature and wildlife. He is frequently commissioned by governments seeking to increase travel and interest in their countries, filming and photographing in North America, South America, Europe, Africa, Asia, New Zealand, and The Galápagos Islands. Hicker specializes in photographs of North America and has spent more than seven years following the seasons in Canada and the United States, with a special focus on Alaska. He now lives in Port McNeill, British Columbia, on the northern tip of Vancouver Island, where he has opened Rolf Hicker Photography, a fine-art photography gallery.

Port McNeill, a “nature lover’s paradise,” provides Hicker with an abundance of photo opportunities. Over the past several years, he worked on a film about killer whales swimming in the waters around Vancouver Island, producing footage that has never been seen or filmed before.

Hicker has received several awards for his work, including the highest award in the “Best Nature Film” category from the prestigious International Film Festival in Dresden, Germany. His photos have been published in magazines such as National Geographic and Reader’s Digest and appear regularly in books, calendars, and other publications.

Whenever he finds the time, Hicker leads exciting photography workshops to locations such as Vancouver Island, Alaska, and New Zealand. His fiancée, Michelle, is a travel writer from New Zealand, and the pair plan to get married there in February. They will be taking an extended honeymoon in Canada and then collaborating on a photography book. You can follow the couple’s exotic travels by visiting their blog: www.travel-location-blog.com.

Sheila Macho
Cover Editor

COVER CREDIT

SOURCE
Interview with the artist.
Assessment of Time and Practice Resources Required to Provide Weekly or Monthly Erythropoiesis-Stimulating Protein Therapy to Chronic Kidney Disease Patients in the Physician Office Setting

MARIALIZA BERNARDO, MD; PAUL CRAWFORD, MD; JOACHIM HERTEL, MD; CHRIS SHOLER, MD; XIAO XU, PhD; THOMAS GOSS, PharmD; RESHMA KEWALRAMANI, MD; and DENISE GLOBE, PhD

ABSTRACT

BACKGROUND: There is an epidemic of chronic kidney disease (CKD) and a high prevalence of anemia (47%) observed in CKD patients. Little is known about the cost in physician office resources of routine erythropoiesis-stimulating protein (ESP) administration to treat patients with nondialysis CKD.

OBJECTIVES: The objectives of this research were (1) to explore the patterns of care in physician offices where nondialysis CKD patients receive routine ESP injections, (2) to examine differences in the monthly resources and related costs incurred by physician offices in treating patients receiving either weekly (QW) or monthly (QM) ESP regimens, and (3) to identify opportunities to minimize the burden of CKD treatment on physician offices.

METHODS: An observational, cross-sectional time and motion assessment was performed in 10 community-based outpatient nephrology practices (5 QW and 5 QM practices); each practice had >40 patients on routine ESP therapy for nondialysis CKD. Three observers trained in health care research documented injection-related tasks and time associated with 91 ESP injection procedures (47 QW and 44 QM) from patients' arrival to and departure from the physician office, office personnel follow-up on billing and documentation, and injection-related staff time. Monthly injection times for QM were calculated by summing the time required to perform the tasks associated with administering a single injection of ESP to subjects, as documented by observers. Total monthly per-patient medical practice costs for providing QM ESP injections were calculated, including labor costs (calculated by applying average wage rates of practice staff to time observed for the specific activities performed) and supply costs (based on average list prices found in medical supply catalogs). Monthly injection times and costs for the QW regimen were calculated by summing the same list of activities as for the QM regimen and multiplying by 4.3 (4.3 weeks per month). Nephrology practice personnel completed a questionnaire summarizing practice characteristics and estimated the time required for some of the injection-related activities. The time and cost associated with each task were analyzed using descriptive and comparative statistics (i.e., Fisher’s exact test and t-test).

RESULTS: On average, patients spent 21 minutes in the clinic for a routine injection visit (QW: 17 minutes, QM: 25 minutes; P = 0.053), during which 11 minutes (52%) were spent interacting with clinic staff (QW: 8.9 minutes, QM: 13.4 minutes; P = 0.005). In the time spent interacting with staff, 3 minutes (QW: 2.9 minutes, QM: 3.6 minutes; P = 0.065) were for dose administration and 8 minutes (QW: 5.3 minutes, QM: 9.8 minutes; P = 0.011) were for staff providing various services to the patients, including registering patients on arrival, examining patients (vital signs, weight, blood work), consulting with patients, and scheduling patients’ next visits. Each month, clinic staff spent a total visit average of 38 minutes providing anemia-related treatment for each QW injection patient, compared with 13 minutes for each QM injection patient (P < 0.001). After patients’ departure, clinic staff spent additional time (not quantified) on billing, filing claims, and other administrative responsibilities most of which could not be observed during our 1-day observation. The average total monthly practice cost of providing ESP therapy to a QW patient ($17.00 [95% confidence interval (CI), 13.00-27.13]) was more than double that for a QM patient ($6.78 [95% CI, 5.34-9.12]; P = 0.004). Differences in visit-related labor costs (QW: $8.34, QM: $3.43; P = 0.108) and injection supply costs (QW: $4.39, QM: $1.67; P < 0.001) accounted for the largest portions of the total monthly cost differential between the treatment regimens. QM dosing would require, on average, 83 hours less staff time and $2,044 less estimated cost treating 200 patients per month compared with weekly administration per clinic.

CONCLUSIONS: Administering routine ESP injections to nondialysis CKD patients for anemia using a QM regimen results in substantial time and cost savings compared with a QW therapy regimen. Managing patients on less-frequent ESP dosing schedules may alleviate medical practice burden by reducing the staff time and supplies related to providing injections in the office.

KEYWORDS: Nondialysis chronic kidney disease, Anemia, Routine ESP administration, Patterns of nephrology care, Resource requirement

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It is estimated that chronic kidney disease (CKD) affects approximately 20 million Americans, with 80,000 newly diagnosed per year. The incidence and prevalence of the disease doubled in the past decade, and the rates reportedly increased in all 50 states over the same time period. Much of the observed increase in CKD stems from epidemic increases in obesity, type 2 diabetes, and hypertension among the U.S. population, with diabetes and hypertension estimated to account for 70% of new cases. Improved treatments for hypertension, diabetes mellitus, and coronary disease have increased longevity in affected patients and, therefore, their likelihood of developing CKD. Regardless of the type of kidney disease, the major

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outcomes of CKD include progression to kidney failure, complications from decreased kidney function, and development of cardiovascular disease. For instance, approximately 20% of patients with severe CKD progress to dialysis.

Although it is well recognized from the third National Health and Nutrition Examination Survey (NHANES) that there is an increasing prevalence of early-stage kidney disease and an increasing incidence of end-stage renal failure, which leads to poor outcomes, CKD is still underdiagnosed and undertreated. To address this issue, the National Kidney Foundation (NKF) Kidney Disease Outcome Quality Initiative (K/DOQI) Advisory Board was tasked to develop clinical practice guidelines to define CKD and to classify stages in the progression of CKD in 2000. The classification and clinical practice guidelines disseminated in 2002 were based on evaluation of the severity of kidney disease, association of level of kidney function with complications, and stratification of risks for loss of kidney function and development of cardiovascular disease. The system classifies individuals into 5 categories, based on glomerular filtration rate (GFR) levels from less severe (Stage I) to most severe (Stage V) (Table 1). GFR may be estimated from serum creatinine and patient characteristics using algorithms including the MDRD (modification of diet in renal disease) or the Cockcroft-Gault formula. The 2006 K/DOQI guidelines defines anemia in CKD patients by a hemoglobin level of <13.5 g/dL in men and 10.5 g/dL in women. Anemia prevalence rises with the worsening of kidney function, from 26.7% of patients in the early stages of CKD to 53.6% in the latest stage of CKD before dialysis.

Anemia is a common complication in CKD patients due to the kidneys’ inability to produce sufficient endogenous erythropoietin, a hormone essential for stimulating the bone marrow to produce new red blood cells and prevent anemia. Approximately half of CKD patients with GFR <60 cc/min/1.73 m² have CKD-related anemia, and anemia has been associated with decreased quality of life (QOL) and increased morbidity, health care costs, and mortality. CKD and anemia combined are thought to be synergistic for adverse health outcomes, particularly for cardiovascular morbidity and mortality.

Importantly, higher hemoglobin levels in CKD patients, both those dependent on dialysis and those not yet on dialysis, have consistently been associated with improved QOL and lower hospitalization and mortality rates. While this association is understood, CKD patients routinely present to dialysis with anemia. Data from the Dialysis Outcomes and Practice Patterns Study (DOPPS) indicated that 27% of patients new to end-stage renal disease treatment received erythropoietin prior to initiation of dialysis, while 66% had a hemoglobin level of <11 g/dL.

The advent of erythropoiesis-stimulating proteins (ESPs) dramatically reduced the use of red blood cell transfusions as the mainstay of therapy for CKD anemia. Epoetin alfa (Epogen), was approved by the U.S. Food and Drug Administration (FDA) for the treatment of anemia in dialysis patients, followed by the approval of ESPs for the treatment of anemia in June 1989 and darbepoetin alfa (Aranesp, in September 2001). However, despite the efficacy of ESPs and Medicare’s willingness to pay for ESPs in patients with hematocrit <33% (after ruling out other treatable causes of anemia), it has been speculated that the low proportion of CKD patients receiving anemia treatment may have to do with the cumbersome frequency of physician visits that is required.

ESP regimens are commonly administered in the outpatient setting, including physician offices and nephrology clinics. Common ESP regimens include dosing frequencies ranging from 3 times per week (TIW) to monthly (QM), depending on patient and physician preference as well as choice of ESP administered. Four recent studies have established the safety and efficacy of QM dosing for darbepoetin alfa and epoetin alfa in the treatment of anemia in CKD patients. The Ling et al. study showed that, for patients initiated on weight-based, every-2-week dosing of darbepoetin alfa, the interval could be extended to QM and the dose was doubled. One of the 4 studies, Disney et al., was an open-label study of darbepoetin alfa. Studies have shown that different ESP dosing regimens routinely achieve comparable clinical results based on achieving targeted hemoglobin levels. Since clinicians perceive different ESP regimens to achieve comparable clinical results, economic and operational factors could influence the therapy and dosing regimen most commonly adopted by nephrology practices and the protocols implemented in these practices.

Currently, little is known about the quantity of medical clinic resources (including time and disposables [e.g., syringes, needles],

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**Table 1: Stages of Chronic Kidney Disease**

<table>
<thead>
<tr>
<th>Stage of Chronic Kidney Disease</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
<th>V</th>
</tr>
</thead>
<tbody>
<tr>
<td>eGFR range</td>
<td>290 ml per minute per 1.73 m² of body surface area with evidence of kidney damage</td>
<td>60-89 ml with evidence of kidney damage</td>
<td>30-59 ml</td>
<td>15-29 ml</td>
<td>&lt;15 ml or dialysis</td>
</tr>
</tbody>
</table>

eGFR = estimated glomerular filtration rate.
but excluding ESP product costs) consumed by administering routine ESP injections to nondialysis anemic CKD patients and whether there is an impact of dosing regimens, particularly dosing frequency, on medical clinic processes and/or burden. According to Crémieux et al., extended dosing intervals could translate into favorable clinical and economic outcomes for patients and caregivers; however, the study did not address the impact of extended dosing on medical clinics. Therefore, knowing this type of information should be helpful to any medical practice with potentially constrained resources, including but not limited to pharmacy-based injection clinics, managed care clinics, and clinics accepting government reimbursement (e.g., Medicaid and Medicare).

The purpose of the Anemia Management Office Resource Evaluation Study was to examine patient-flow characteristics and assess patterns of care in clinics where nondialysis CKD patients receive ESP therapies. The study is intended to identify the overall impact of routine ESP administration on practice burden and to assess the impact of ESP injection administration dosing frequency on the practice burden in terms of monthly injection administration time and monthly injection-related supply costs, excluding ESP costs.

### Methods

#### Study Design

An observational, cross-sectional time and motion study was conducted to assess practice resources related to ESP injection. A convenience sample of 10 nephrology practices that treated at least 40 CKD patients (a relatively high volume) with a standard QM or QW (weekly) ESP regimen was included in the assessment. Five sites routinely administering ESP QM and 5 sites routinely administering ESP QW were selected for comparability of patient volume for the 2 regimens according to the following site selection criteria:

- Outpatient CKD clinic administering ESP QM or QW in the office with ≥40 patients receiving one or both regimens
- Willingness to allow time and motion observation of ESP-related practice activities
- Willingness to complete a brief practice survey

Selection of sites with comparable volumes of patients receiving ESP therapy was required to reduce the risk of bias associated with scale economies. Time and motion observation data were collected from June through September 2005. The study protocol was approved by an accredited central human institutional review board (IRB).

QM and QW regimens were defined by the dosing interval only, not by the product. The ESP injection could be any type of ESP drug. The observations that we recorded at each site were either QM or QW at a particular site even though some of the sites administered ESPs at both dosing intervals. Given that only 1 regimen was observed at each site, we thus classified the sites as QM or QW in this study.

#### Data Collection

Three researchers (observers), each with 2 to 4 years of health services research background, received standardized training on observing and recording times associated with various standard activities associated with ESP injection administration. The standardized 6-hour training included reviewing the study protocol, observation process, and practice flow; practicing time recording by watching injection videos; comparing documented times across observers and trainers; and analyzing the differences. The trained observers went to each site in pairs for a 1-day observation and observed all the injections throughout the entirety of the injection clinic schedule for the day on which the office observation was scheduled. Activities and time were recorded from each patient’s arrival in the clinic/office until the patient’s departure. After the patient’s departure, activities related to the injection, such as billing, were followed and recorded. To control for possible observer bias by treatment regimen, reasonable efforts were made to ensure that observers were “blinded” to regimen. Specifically, the trained observers were not provided a priori information concerning the type of ESP used or the frequency of patient dosing in the practice while they were on site to conduct the time and motion assessment. The study coordinators and staff working with the observers were trained not to inform the observers; the intent was for these observers to be unbiased with regard to the treatment regimen. A total of 44 QM injections were observed in the QM sites, and 47 QW injections were observed in the QW sites. To assess interrater reliability, the extent of the consensus among the observers, 2 trained observers at each site observed 10% of the injections (1 injection per site) concurrently. The injection to be observed concurrently was selected based on random number lists generated a priori (assuming an average of 8 injections to be observed per site).

#### Time and Motion Task List

A standardized task list was developed and used to record times in minutes and seconds. Data collected during the time and motion assessment included the number of injections scheduled for the same time slot, time of day the injection was administered, patient sign-in and sign-out time, injection-related clinical activities, injection-related administrative activities, clinical supplies used, providers seen during visit, and reimbursement-related activities.
The injection-related clinical and administrative activities were grouped into 5 main categories:

1. **Visit-related activities.** Greeting patient and taking him/her to the exam room, taking vital signs/blood pressure, weighing patient, taking blood samples, consulting by physician, dismissing patient

2. **Dose administration-related activities.** Reviewing patient chart and confirming dose, obtaining product from central storage area, preparing injection, administering injection, disposing of waste, documenting ESP injection

3. **Front office-related activities.** Scheduling appointments, rescheduling appointments, appointment reminder calls/cards, arranging travel for ESP patient, registering patient on arrival, pulling patient chart, filing labs into patient chart, filing ESP records into patient chart, refiling patient chart

4. **ESP-related financial activities.** Preparing bills, recording payments, filing claim, making calls to payers, preparing supporting documentation

5. **Other ESP-related activities.** Counting and ordering ESP inventory, stocking ESP inventory, making holiday arrangements for patient, recording and delivering iron prescriptions

Any activities observed that were not on the standard checklist were recorded under “other” where room was provided for a brief description. Patients’ waiting time also was documented. In addition, supplies used in the ESP administration, such as gloves, alcohol swabs, needle, and syringe, were documented in the task list.

**Practice Questionnaire**

Each investigator also completed a questionnaire assessing specific nephrology practice characteristics, including practice size,
Assessment of Time and Practice Resources Required to Provide Weekly or Monthly Erythropoiesis-Stimulating Protein Therapy to Chronic Kidney Disease Patients in the Physician Office Setting

### Methods of Analysis

Monthly injection times for QM were calculated by summing the observed time required to perform the tasks associated with administering a single injection of ESP to nondialysis CKD subjects, which included injection-related clinical activities (visit-related activities and dose administration-related activities) and injection-related administrative activities (front office-related activities, ESP-related financial activities, and other ESP-related activities). We were only able to observe ESP-related financial activities (e.g., filing claim, making calls to payers) for 2 injections and to observe counting and ordering ESP inventory at 1 site. Most of these activities occurred at different locations and/or times other than the days when we conducted on-site observations. Given the limited observations, we did not include time associated with these tasks in our total ESP-related time calculation. Monthly injection times for the QW regimen were calculated by summing the same list of activities as for QM regimen and multiplying by 4.3 (4.3 weeks per month). To compare perceived time with actual time spent on various activities, we compared the practice-reported injection time as estimated by the study coordinator at each study site to the actual injection time measured by the observer.

Total monthly per-patient practice costs for providing ESP injections were calculated using labor costs and supply costs. The labor costs were calculated by applying average wage rates of practice staff to time observed for the specific activities.
Assessment of Time and Practice Resources Required to Provide Weekly or Monthly Erythropoiesis-Stimulating Protein Therapy to Chronic Kidney Disease Patients in the Physician Office Setting

performed. We used standardized national wage rates from the 2005 U.S. Department of Labor/Bureau of Labor Statistics, National Compensation Survey, and salary.com to assign practice staff wage rates. The supply costs were based on average list prices found in medical supply catalogs. The costs of resources used as determined by the activities and supplies listed above were summed to calculate QM costs, while the monthly costs for QW were calculated by summing the costs of the resources observed (reported) per injection and multiplying by 4.3 (52 weeks per year/12 months per year). This method of calculation has been widely used in other studies, including studies reported by Foster et al. in the Journal of the American Medical Association.

Summary statistics (n, mean, standard deviation [SD], median, and range) were calculated for the continuous variables (e.g., monthly practice-level injection administration time, monthly practice-level billing time, and monthly cost of practice resources used). Frequency distributions were reported for the categorical outcomes (e.g., sex, employment status preference for ESP regimen). Differences between treatment groups were compared using Fisher's exact test for categorical variables and the t test or Wilcoxon test for continuous variables.

The interrater reliability among the observers was calculated using 2 methods. First, for all the tasks, we established consensus (measured as the number of agreements [observed/not observed] divided by the total number of observations) and reported as a Kappa statistic. By convention, a Kappa of 0.40 to 0.59 is considered moderate interrater reliability, 0.60 to 0.79 is considered substantial interrater reliability, and 0.80 is considered outstanding interrater reliability.

To assess how similar the observed times were between observers for each activity and to what extent the observers agreed on the length of time taken for each observed activity, we calculated the intraclass correlation (ICC). The interpretation of ICC is similar to Kappa.

### Results

We screened 232 nephrology practices to identify 15 sites that...
were interested and able to participate in the study and could use a central IRB. Among these 15 sites, we selected 10 large sites that met study inclusion criteria. Table 3 summarizes the participating study site characteristics by treatment regimen (QW vs. QM). These practice demographics provide several important insights on nephrology practices treating CKD patients with anemia. On average, 254 patients were receiving ESP therapy at each site (218 at QW sites and 292 at QM sites). Among the practices, 80% (4/5 QW and 4/5 QM) reported using a specific “injection clinic” day or time to manage routine ESP injections. The QW sites reported designating an average of 10 hours per week, while QM practices reported designating an average of 24 hours per week for injection clinics. On a typical day, QW sites provided 24 injections and QM sites provided 20 ESP injections. All the sites participating in this study were accepting new patients. None of the differences between QW and QM sites reached statistical significance.

Time Assessments

We observed 91 ESP injections—47 in the QW practices and 44 in the QM practices—and when we assessed consensus in activities observed and time recorded between the observers, we observed a high degree of interrater reliability (Kappa = 0.81, ICC = 0.79) among the observers. There were differences between QW and QM sites in the relative frequency in which routine activities were performed as part of a visit in which an ESP injection was administered, including weighing the patient, taking blood pressure/vital signs, taking blood for laboratory analysis, and providing physician consultation (Figure 1 A-D). For example, taking blood pressure/vital signs was not routinely performed in 23% of QW observations compared with only 2% of the QM observations (P = 0.004). Physician consultation was only observed in 4% of QW patients but in 21% of QM patients (P = 0.024). There also was a substantial variation in the time spent on injection-related activities between QM and QW injection sites on a per-injection basis (data not presented). For example, the time spent administering an injection took only half a minute for the QW regimen but 1 minute for the QM regimen (P < 0.001). Among patients who received physician consultation, the average consultation time was 7.8 minutes per QM patient but 5.2 minutes per QW patient (P = 0.684).

Figure 2 summarizes the observed time per patient per month spent on injection-related activities. Each month, nephrology practices spent a mean (SD) of 38.2 (33.1) minutes with each QW patient (8.9 minutes at injection level) compared with 13.4 (7.3) minutes with each QM patient (P < 0.001 for comparison at monthly level; P = 0.0048 for comparison at injection level). Further, QW and QM sites reported 150 and 87.5 (median) additional minutes per patient per month, respectively, for administrative tasks related to ESP injections, which were not observed directly by the trained observers. We note that the relationship between QM and QW injections is not linear (i.e., QW injections do not require 4 times the time observed for 1 QM injection on a per-patient per-month basis).

Per month, patients on QW regimen spent 74.8 minutes in nephrology clinics receiving their ESP injections, while patients on QM regimen only spent a total time of 24.8 minutes (P < 0.001, Figure 2). Patients receiving ESP injections spent a substantial amount of time waiting and on activities other than receiving the injection. Overall, patients spent a mean (median) time of 21 (19) minutes in the clinic for a routine injection visit (mean: QW: 17 minutes, QM: 25 minutes; P = 0.053). During this time, 3 minutes (QW: 2.9 minutes, QM: 3.6 minutes;
P = 0.065) were spent interacting with clinic staff for dose administration (reviewing chart, confirming dose, preparing and administering injection, disposing of waste, and documenting injection) and 8 minutes (QW: 5.3 minutes, QM: 9.8 minutes; P = 0.011) were spent on staff providing various services to the patients, including registering patients on arrival, examining patients (vital signs, weight, blood work), consulting with patients, and scheduling patients’ next visits. The other 10 minutes were spent on waiting (QW: 8.8 minutes, QM: 11.6 minutes; P = 0.319).

Observer-Questionnaire Agreement

Some ESP-related activities, such as rescheduling appointments, front-office preparation for injection for patient, and actual ESP injection, were both observed and estimated by practices. The sites consistently overestimated the time spent on routine injection-related activities by a substantial amount (Figure 3). For example, the practices estimated spending 7 minutes preparing medication to completing administration and waste disposal for QW injection and 15 minutes for QM injection per injection, but only 2.7 minutes for QW injection and 3.4 minutes for QM injection were observed.

Practice Costs

One of the main objectives of this study was to estimate the monthly costs of administering ESP regimens from the nephrology practice perspective. The mean (SD) total monthly nephrology practice cost of providing ESP therapy to a QW patient ($17.00 [21.80]) was more than double that for a QM patient ($6.78 [6.20]), respectively, for activities observed in this study. A summary of the components of the monthly cost of providing an ESP regimen is provided in Figure 4. Mean costs were different between the QM and QW groups for total monthly injection-related practice costs (P = 0.004), labor costs of visit-related (P = 0.108), dose administration-related (P < 0.001), and front office-related activities (P = 0.005), and injection-related supplies costs (P < 0.001). As mentioned earlier, since most of the other ESP-related activities (i.e., ordering and counting ESP inventory) and financial activities (i.e., filing claims, making calls to payers) occurred at different locations and/or times other than the days when we conducted on-site observations, the labor costs estimates associated with practice staff time did not include time of these 2 categories of activities.

Discussion

This is one of very few studies to collect empirical data on activities and resource utilization associated with routine ESP administration from nephrology practices (outpatient clinics and physician offices) administering in-office ESP therapy and the only study to our knowledge to report these data from nephrology offices on nondialysis CKD patients. Our study observed that the average number of ancillary personnel at the QW sites was almost 100% higher than at the QM sites, while the average number of patients seen per day was only about 26% higher. Further, the number of patients on ESP therapy at QM sites was about 34% higher compared with QW sites.

Management of CKD patients generally includes monitoring patients’ vital signs, weight, and lab results and adjusting therapy accordingly. Although we observed that these activities were not necessarily performed routinely at each injection visit, they were performed in a larger proportion of observed QM injections compared with QW injections. In this study, there was no evidence that more frequent office visits for injection resulted in more comprehensive care. While this study provides an overview of the activities and staff resources used during routine ESP injection visits, there was a notable variation in the average time spent per injection: staff spent an average of 13 minutes interacting with QM patients while only 8.9 minutes with QW patients per injection. The relationship between QM and QW injections is not linear (i.e., QW injections do not require 4 times the time observed of 1 QM injection on a per-patient-per-month basis). Patients treated with a QM regimen spent more time with their physicians, nurse practitioners, and nurses for their consultation compared with patients on a QW regimen (4% of QW [equivalent to 17% QM] and 21% of QM patients had a physician consultation observed, with the mean observed time being 5.2 minutes for QW patients and 7.8 minutes for QM patients).

The average number of patients receiving injections in the observed nephrology practices each month was more than 200. Each month, nephrology practices spent a mean of 38.2 minutes with each QW patient and 13.4 minutes with each QM patient.
Considering the number of patients receiving injections, the nephrology practices spent 82.7 more hours per month performing observed injection-related activities to treat 200 QW patients compared with 200 QM patients. Stated another way, the observed staff time required to administer QW injections to 200 patients each month is equivalent to the observed staff time required to administer QM injections to 570 patients, which suggests that switching from a QW to a QM injection schedule could increase nephrology practice capacity by 185% in a practice treating 200 patients per month. Also, at a monthly level, the total monthly nephrology practice cost was twice as high for providing QW regimen compared with QM regimen (mean cost: QW $17.00, QM $6.78). To put the estimates in the context of the number of patients receiving injections in a busy nephrology practice treating 200 patients per month, the medical practice would have incurred an estimated $2,044 more in total monthly practice costs when providing QW ESP therapy compared with a QM regimen.

On the basis of the findings from the present study, in estimating time savings for providing ESP injections to a hypothetical clinic size of 200 patients on a cumulative monthly basis, QM dosing would require, on average, 83 fewer hours of staff time and $2,044 less cost per month compared with QW. It is possible that the time saved could be used to see other CKD patients or to provide other components of CKD care. CKD clinics that provide comprehensive care for anemia management provided by nurse practitioners have reported positive outcomes of slowed progression of CKD among patients, and improved blood pressure control, medication compliance, and diabetes self-management skills. With the practices having more time, more comprehensive and quality care could be provided to patients to improve their overall health and well-being.

Given that some of the activities (such as billing and inventory) were not observed, the actual medical practice burden is likely greater than the time and costs presented in this study. The unobserved time (e.g., practice preparation time, retrieval of laboratory results) could not be included because this information could not be collected accurately at the patient level. In addition, our estimate of medical practice costs (based on time, labor, and disposables) clearly excludes the costs associated with practice overhead and malpractice insurance expenses. The overall weighting of the relative value unit (RVU) for typical physician services comprises 3 factors: a work component (approximately 30%-35%), practice expense component (approximately 63%-68%), and physician liability insurance component (2%-3%) for common injection and level 1 evaluation and management codes. The payment rate for a routine administration (Current Procedural Terminology [CPT] code 90772) is approximately $18.57 per injection, and CPT code 99211 is approximately $21.60, according to the 2006 Medicare Physician Fee Schedule from the Centers for Medicare and Medicaid Services (CMS).

Using the RVU proportion of the work component, medical practices are reimbursed from $5.57 to $7.56 per injection for injection-related work. The time observed in the practices represented only a proportion of the staff work time per injection. Thus, the current reimbursement rate may be insufficient for the amount of work associated with administration practices for injections.

An important observation from the current study is the apparent discrepancy between practice-reported estimates of time spent on activities, which were both observed directly by the trained observers and self-reported by the medical practices. For the ESP injection-related activities that were both recorded by observers and reported by practice staff, sites overwhelmingly and consistently overestimated the time spent on routine injection-related activities, possibly because practice staff had a difficult time separating out time for discrete tasks. This finding is consistent with the finding from another time and observation study reporting physician activities during time out of the examination room. Given that the nephrology practice personnel overestimated the resources required for routine ESP administration, they might underestimate their capacity to treat nondialysis CKD patients, which validates the need for studies like this.

Limitations

While the sample size studied was sufficient to observe some of these important differences between QM and QW regimens, it is possible that other important differences may not have been observed and that the results cannot be generalized to all sites providing ESP therapy to CKD patients. First, this study focused on sampling large nephrology practices to ensure its timely completion. A broad sample of sites was contacted to assess interest in participation; however, the participation rate was quite low due to the criterion of selecting large nephrology practices that currently had, on average, at least 40 CKD patients with anemia requiring ESP injections. The time observed might underestimate the actual activity time, given that the participation sites might be more efficient in injection-related activities because of high patient volume.

Second, this is a convenience sample because the clinics volunteered to participate. It is possible that these sites may differ in some unknown ways from other CKD practices that routinely provide ESP therapy. On one hand, we are aware that our trained study observers were in the nephrology practices for only 1 day per practice site, and it is possible that the injections we observed are not able to be completely generalized to the nephrology practices on other days. On the other hand, convenience samples have been frequently used in published research. According to Kalton, most behavioral and social science studies use convenience samples consisting of students, paid volunteers, and patients. Studies with such samples are useful primarily for documenting that a particular characteristic or phenomenon occurs within a given group or,
Alternatively, for demonstrating that not all members of that group manifest a particular trait. Such studies are also very useful for detecting relationships between different phenomena. As this study was based on a convenience sample, *P* values from inferential statistics should be interpreted carefully.

A third potential limitation to this study includes the fact that we preselected the injection intervals to study. We know that other common regimen frequencies, such as Q2W, Q3W, and Q5W (every 2, 3, and 5 weeks, respectively), would be of interest and relevant to the practicing nephrology community, but these dose regimens were beyond the scope of the current study and would have added complexity and cost to study design and execution. We also note with interest that this study provided sufficient data for us to conclude that the time and costs associated with these other regimens wouldn’t simply be linear relative to the QW regimen (i.e., 2, 3, or 5 times the time and costs associated with the QW regimen). Fourth, where the injection-related activities were not observed, practice-reported data may overestimate the time (and therefore the costs) associated with some injection-related activities.

While we note these limitations, we believe that the overall study results provide new and meaningful data to help CKD practices inform the selection of ESP regimens to help improve practice efficiency while ensuring high quality of care and the effectiveness of the overall delivery of anemia management to nondialysis CKD patients.

### Conclusions

This study provides an overview of the activities and staff resources required during routine QW and QM ESP injection appointments. This study documents that CKD patients on ESP therapy spend substantial amounts of their time in nephrology practices, regardless of treatment regimen. The information from this study may be used to identify clinic practices that improve efficiency in managing nondialysis CKD patients, minimizing both patient and clinic staff time while providing similar or improved patient care.

Practices spent approximately two thirds less time per month with patients on QM ESP therapy than with patients on QW therapy. Extended ESP dosing reduces the time burden of CKD clinic staff and can provide opportunities to perform comprehensive patient care activities. Staff estimates of time differed significantly from observed time, underscoring the importance and the benefit of directly measuring the impact of these common activities. Given the differences we observed between routine QW and QM ESP administration in busy nephrology practices, nephrology clinics could realize potential benefits associated with more evidence-based resource planning.

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### What is already known about this subject

Currently little is known about the quantity of medical clinic resources consumed by administering routine ESP injections to nondialysis anemic CKD patients.

### What this study adds

This study assessed professional time and costs associated with routine ESP therapy and provides an estimate of resource costs associated with ESP dosing frequency.

### DISCLOSURES

Funding for this research was provided by Amgen, Inc. Members of the research team included participants from the sponsor who also met the criteria to participate as coauthors. Members of the sponsor team disclose that they have been involved in all aspects of this project from study design to manuscript preparation but have not unduly influenced the objectivity of the study analysis, data interpretation, or report of the results. Authors Reshma Kewalramani and Denise Globe are employees of Amgen, Inc., and own Amgen stock and stock options. Authors Manaliza Bernardo, Paul Crawford, Joachim Hertel, and Chris Sholer were investigators in the current study and received compensation from Amgen, Inc. for their work; authors Xiao Xu and Thomas Goss are employees of Covance Inc., the company that held the contract for conducting the study funded by Amgen, Inc.

Bernardo served as principal author of the study. Study concept and design were primarily contributed by Kewalramani and Globe, with input from the coauthors. Data collection was the work of Bernardo, Crawford, Hertel, and Sholer; data interpretation was primarily the work of Xu and Goss, with input from the coauthors. Writing of the manuscript and its revision was the work of all authors, with primary input from Globe and Kewalramani.

###REFERENCES

Assessment of Time and Practice Resources Required to Provide Weekly or Monthly Erthropoiesis-Stimulating Protein Therapy to Chronic Kidney Disease Patients in the Physician Office Setting


ABSTRACT

BACKGROUND: Promoting use of pharmacoeconomic models by formulary reviewers is a goal of the Academy of Managed Care Pharmacy (AMCP) Format for Formulary Submissions, but relatively few decision makers use such models, and many doubt that they provide meaningful input.

OBJECTIVE: To demonstrate how sophisticated disease-based pharmacoeconomic models can aid formulary decision makers when long-term outcomes data are lacking.

METHODS: The Center for Outcomes Research (CORE) Diabetes Model (CDM), a published, validated Markov pharmacoeconomic model that projects clinical and economic endpoints, was used to model the cost-effectiveness of exenatide, a new injectable antidiabetic agent that enhances glucose-dependent insulin secretion, in a standard cohort of type 2 diabetes patients (mean body mass index [BMI] = 27.5 ± 3 kg/m²), compared with a modified obese cohort (mean BMI = 35 ± 3 kg/m²) that was otherwise demographically identical at baseline to the standard cohort. The standard cohort was assumed to maintain baseline weight during treatment, and the modified obese cohort was assumed to experience weight loss of approximately 9% (mean = 3 kg/m²), with corresponding improvements in blood pressure, low-density lipoprotein cholesterol, and triglycerides. We selected a 30-year time horizon because it was the time interval during which the CDM predicted most of the subjects would have died, and the costs obtained thus reasonably projected lifetime total direct medical costs for these cohorts. While treatment options certainly will change over a 30-year period, our goal was to estimate the incremental effect of exenatide over other available therapies.

RESULTS: The model predicted reduced long-term treatment costs in obese patients, driven by an 11% decrease in cardiovascular disease burden and derived from the presumed weight loss. The incremental cost-effectiveness ratio (ICER) for adding exenatide over 3 years was $35,000/quality-adjusted life-year (QALY). Using a 30-year horizon, ICER values were $13,000/QALY versus insulin, $32,000 versus generic glyburide, and $16,000 versus no additional treatment. Exenatide dominated pioglitazone. By comparison, the 30-year ICER for exenatide versus insulin was $32,000 versus generic glyburide, and $16,000 versus no additional treatment. (QALY). Using a 30-year horizon, ICER values were $13,000/QALY versus insulin, $32,000 versus generic glyburide, and $16,000 versus no additional treatment. Exenatide dominated pioglitazone. By comparison, the 30-year ICER for exenatide versus insulin was $32,000 versus generic glyburide, and $16,000 versus no additional treatment. Exenatide dominated pioglitazone. By comparison, the 30-year ICER for exenatide versus insulin was $32,000 versus generic glyburide, and $16,000 versus no additional treatment.

CONCLUSIONS: Disease-based pharmacoeconomic models may help third-party payers project costs and be particularly useful when only data from short-term clinical trials are available. In the present case, the pharmacy staff of a health plan used a pharmacoeconomic model for drug treatment of type 2 diabetes provided by the manufacturer as part of the AMCP Format dossier process to project cost outcomes for exenatide, adjunct injectable therapy for patients taking metformin and/or sulfonylurea. The P&T committee approved the drug for inclusion in the drug formulary based in part on the results of the pharmacoeconomic model produced from the cost inputs entered into the model by the health plan pharmacists.

KEYWORDS: Exenatide; Pharmacoeconomic models; Drug formulary; AMCP Format

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SINCE THE FIRST PUBLICATION OF THE ACADEMY OF MANAGED CARE PHARMACY (AMCP) FORMAT FOR FORMULARY SUBMISSIONS IN 2000, ONE OF ITS GOALS HAS BEEN TO ENCOURAGE THE MEANINGFUL CONSIDERATION OF PHARMACOECONOMIC MODELING RESULTS AS PART OF THE FORMULARY REVIEW PROCESS.1 THE INFORMATION THAT CAN BE GLEANED FROM WELL-DESIGNED MODELS EXTENDS FAR BEYOND SIMPLY PROJECTING THE FISCAL IMPACT OF A NEW PRODUCT ON PHARMACY BUDGETS. IT SUGGESTS THE EXTENT TO WHICH DRUG COST MAY BE OFFSET BY REDUCTIONS IN OTHER MEDICAL COSTS, EVALUATES COST-EFFECTIVENESS OF THE NEW TREATMENT, AND IN SOME CASES HELPS IDENTIFY TARGET SUBPOPULATIONS IN WHOM THE DRUG WILL HAVE A GREATER BENEFIT AND/OR A SMALLER NUMBER NEEDED TO TREAT (NNT), THUS IMPROVING INCREMENTAL COST-EFFECTIVENESS RATIOS (ICERS) IN SUCH PATIENTS. THE IMPORTANCE OF ECONOMIC MODELS WILL INCREASE AS MORE BIOLOGICS AND OTHER HIGH-COST MEDICATIONS COME TO MARKET SINCE THERAPEUTIC SELECTION OFTEN INVOLVES CHOICES AMONG DRUGS THAT ARE COVERED UNDER BOTH PHARMACY AND MEDICAL BENEFITS BY MOST U.S. PAYERS. IN THIS ENVIRONMENT, HEALTH PLAN PHARMACY BENEFIT MANAGERS WILL REQUIRE SOUND DATA TO PERSUADE ACTUARIES, BROKERS, CUSTOMERS, HEALTH PLAN CHIEF FINANCIAL OFFICERS, AND OTHER EXECUTIVES OF THE NEED TO EXPAND PHARMACY BUDGETS BASED ON DEMONSTRATED MEDICAL COST OFFSETS.

Many emerging drugs are designed to treat chronic conditions and will be taken over many years, perhaps for the lifetime of the patient. In such cases, some of the most important proposed benefits of the drug cannot be measured in clinical trials because they will not be observed for years or decades. The budget impact of new drugs and other technology will become increasingly important, and payers will demand more than theoretical projections to support the proposed value of these agents. Until evidence can be accumulated in administrative

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claims or from postmarketing clinical studies, sophisticated disease-based economic models can be substituted. For this reason, payers and policymakers need to consider providing appropriate incentives to encourage improved modeling efforts.

Monitoring the value of drugs used to treat type 2 diabetes will provide excellent opportunities to apply advanced pharmaco-economic modeling technologies. The aging population will increase the prevalence of individuals at risk of developing this disease. Use of these drugs will be increased further by shifts in diabetes clinical practice guidelines toward earlier diagnosis and more aggressive treatment, with the result that more individuals will be treated with more drugs for longer portions of their lives. Meanwhile, several new classes of drugs are appearing: inhaled insulins (Exubera), incretins (exenatide and liraglutide), and the new class of dipeptidyl peptidase IV inhibitors (sitagliptin and vildagliptin). With all these changes, payers will face complex formulary choices and will need to consider appropriate step-therapy algorithms.

Langley and Sullivan first published guidelines for pharmaco-economic evaluation by U.S. private payers in 1996. From this concept, Mather et al. drafted a set of guidelines for implementation at Regence BlueShield, where the guidelines improved the efficiency of the evidence-gathering process employed by the plan’s pharmacy staff. Although the pharmaco-economic modeling presented in these early dossiers left much to be desired, it was a step in the right direction.

Upon publication of the first version of the AMCP Format in 2000, Premera Blue Cross, a 1.6- million-member commercial participating provider option health plan operating in Washington and Alaska, adopted a similar process in 2001. Premera pharmacy staff has archived all dossiers and economic models received since that time for formal evaluation, preliminary results of which suggest that the quality of the dossiers continues to be inconsistent. The quality of dossiers does seem to be better for innovative products, and a number of useful models have been submitted; the results have been included in the formulary decision-making process at Premera. The AMCP Format includes a synthesis of modeling standards developed by the Panel on Cost-Effectiveness in Health and Medicine and will be updated to reflect the ongoing work of others, such as the International Society for Pharmacoeconomics and Outcomes Research (ISPOR).

Many health plans now use the AMCP Format as a tool to improve efficiency in gathering clinical information, but relatively few decision makers give serious consideration to the models offered with product dossiers. There is a perception that these models do not provide useful input to the average managed care organization (MCO). Several reasons for this have been suggested. Many MCO pharmacists believe that manufacturer-sponsored economic evaluations will be biased toward the product being evaluated. There is some evidence to support this belief. A recent systematic review of published analyses reported an odds ratio of 2:1 that the product would cost less than $20,000 per quality-adjusted life-year (QALY) gained when the manufacturer had funded the study. In our experience, although one can become reasonably adept at spotting the most obvious biases without extensive pharmaco-economic training, most health plan formulary support personnel have yet to attempt this on a regular basis. Other reasons for the lack of use of modeling include perceived lack of relevance, sociocultural attitudes, and a lack of understanding of the methodology and lack of expertise needed to evaluate models.

From these empirical observations, it is evident that dossier models must adapt to a variety of skill levels among the target audience, and assumptions biased toward the product must be eliminated. Furthermore, the attributes of different health plans and the conditions under which managed care pharmacists conduct formulary reviews vary considerably. These factors make customization of the model presentation and input variables for the individual health plan a necessity. This customization is a 2-way process. The model builder and the end user must communicate clearly if the customized model is to have a reasonable chance of meeting the customer’s needs.

The foregoing discussion demonstrates that economic modeling can meet a variety of customer needs for budget and cost-effectiveness forecasting, but it should be noted that a well-designed disease-based model can predict long-term clinical outcomes as well. Especially with newer drugs, it is often the case that the most important clinical outcomes of the therapy have not been experimentally verified. In some cases, the required clinical trials can never be performed because they would involve exposing subjects to ethically unacceptable levels of risk or to treatments whose efficacy is known to be less than proven alternatives. Moreover, these clinical trials would need to run 10 to 15 years or longer, making them prohibitively expensive for most manufacturers. When experimental data are lacking or ambiguous, models can sometimes be used to predict the relevant outcomes. Both developer and end user should be aware of the limitations of such use, and they should carefully evaluate the assumptions, particularly when projecting long-term outcomes from short-term data.

The challenge of modeling a new product for which there are no long-term study results becomes even more difficult when the manufacturer is inexperienced in presenting pharmaceutical outcomes to the customer. The biotechnology revolution has opened the door for many smaller innovative companies to develop potentially valuable products. Such companies may license or co-market the product through a more experienced vendor, but doing so is certainly not a requirement. Consultants are available to assist them in developing meaningful outcomes presentations that articulate the value of the new product. In fact, a creative manufacturer may be in a better position to develop new ways of demonstrating a product’s value since the manufacturer does not have old templates or historical inertia.

Amylin Pharmaceuticals, a biopharmaceutical manufacturer,
Exenatide is approved by the FDA for use as
of this model.

Methods

Setting
In 2001, Premera Blue Cross established an independent
formulary review process based on the AMCP Format. Pharmacists review the manufacturer's dossier, conduct
independent literature research, and prepare evidence
summaries in the form of formulary monographs. The P&T
commitee members, leading physicians and pharmacists from
various parts of Washington and Alaska, select formulary products,
determine the positioning of products in copayment tiers, and
approve criteria to determine medical necessity. No voting
member of this committee may be a regular employee of
Premera or have a financial interest in any health plan. Members
declare conflicts of interest before product discussions and then
refrain from voting in that instance.

Amylin Pharmaceuticals is a biopharmaceutical company
specializing in genetically engineered peptides, the first two of
which, exenatide and pramlintide, were approved by the U.S.
Food and Drug Administration (FDA) in 2005. Before launching
these products, Amylin made a significant research effort to
determine customer requirements, including the need for
pharmacoeconomic modeling, by conducting market surveys,
advisory board meetings, and individual interviews with key
customers.

Exenatide
Exenatide is the first incretin agent that mimics the enhance-
ment of glucose-dependent insulin secretion and several
other antihyperglycemic actions of incretins, a group of
hormones that are released into the circulation by the gut. First
discovered in the saliva of Gila monsters, it is now produced
synthetically. Exenatide is approved by the FDA for use as
adjunctive therapy to improve glycemic control in patients with
type 2 diabetes mellitus who are taking metformin, a sulfony-
lucrea, or a combination of metformin and a sulfonylurea, but
have not achieved adequate glycemic control. Along with small
reductions in glycosylated hemoglobin (HbA1c) levels (0.5-0.9),
a statistically significant maximum weight loss of 2-3 kg from
baseline body weight was observed in exenatide clinical trials. Compared with placebo (metformin alone), exenatide in
combination with metformin at 30 weeks of follow-up was
associated with a net weight loss of 1.3 kg (1.3%) at the 5-mg
dose twice daily or of 2.5 kg (2.5%) at the 10-mg dose twice
daily. Weight loss was less for exenatide in combination with
sulfonylurea. For exenatide in combination with metformin and
sulfonylurea, the mean weight loss at week 30 was only 0.7 kg
(0.7%) for either 5 mg twice daily or 10 mg twice daily,
compared with placebo.

Various studies have examined the effect of weight loss on
cardiovascular risk factors such as blood pressure and lipid levels.
In 2003, Anderson et al. published a systematic review and
meta-analysis of these studies, from which they predicted that a
10% reduction in body weight would produce decreases of 11%
in low-density lipoprotein cholesterol (LDL-C), 26.7% in
triglyceride levels, and 8.1% in systolic blood pressure.

Notwithstanding the extent to which exenatide is discussed
in this paper, the following should not be construed as
advocating its use over that of any other competing antidiabetic
agent. Our intent is rather to demonstrate how economic
modeling was used to support the manufacturer's application
for formulary review. However, submission of a dossier with
cost-effectiveness modeling does not guarantee review of any
product by the Premera P&T committee.

CORE Diabetes Model
We employed the CDM, a published, validated Markov process
model that uses surrogate clinical endpoints, such as HbA1c,
LDL-C, and body mass index (BMI) to project long-term
clinical endpoints such as myocardial infarction, stroke, end-
stage renal disease, neuropathy, and retinopathy. The CDM also
projects economic endpoints, of which drug cost, total cost of
care, life expectancy, and QALY are of greatest interest to our
formulary reviewers. Previous publications have described the
structure, data inputs, and validation of this model.

Other validated models have also been published, including
the Archimedes model and others that use newer methodology.
Premera does not advocate the use of any particular model
because all of them are capable of performing the analysis
required for our project. It is not the purpose of this report to
critique these models; however, we did take the limitations of the CDM and of Markov models in general into consideration.

The CDM is consistent with recently published American Diabetes Association computer-based modeling guidelines and principles for diabetes.\textsuperscript{19} HbA1c-dependent adjustments for the risks of developing complications in type 1 diabetes mellitus were derived predominantly from the Diabetes Control and Complications Trial\textsuperscript{20} and for type 2 diabetes mellitus from the United Kingdom Prospective Diabetes Study (UKPDS).\textsuperscript{21} Other studies used to construct the CDM have been previously described.\textsuperscript{16}

The CDM predicts the development and progression of type 2 diabetes over varying time horizons (1-100 years), using best available published clinical and epidemiological data. The model has a standard Markov structure, combined with Monte Carlo simulation and the use of tracker variables, that allows for the development and progression of multiple complications in an individual patient over time, while at the same time overcoming the memory-free properties of traditional Markov models.

A Markov model consists of a series of states corresponding to clinical situations, e.g., healthy, ambulatory ill, or hospitalized. Each state is populated with a certain number of hypothetical patients. The model repeats a number of cycles, with individuals moving from one state to another at each cycle, on the basis of transition probabilities determined from epidemiological or clinical studies. When an individual moves to a particular state, a traditional Markov model has no memory of the path that individual took to get there. This is a major limitation when modeling a long-term chronic disease such as diabetes, but the CORE model works around this by storing the information in tracker variables. Incidence and progression of comorbidities can thus be followed and coordinated with the main diabetes model. The process of deciding which transition probabilities and risk adjustments from the published literature to incorporate into the CDM was undertaken by a multinational expert panel comprising 2 health economists and 4 physicians convened by the model developers, and is described in detail elsewhere.\textsuperscript{16}

The CDM structure includes 15 submodels that simulate diabetes-related complications (angina, cataract, congestive heart failure, foot ulcer and amputation, hypoglycemia, keto-acidosis, lactic acidosis, macular edema, myocardial infarction, nephropathy, neuropathy, peripheral vascular disease, retinopathy, and stroke) along with all-cause mortality. All submodels run parallel to each other to allow hypothetical patients to develop complications concomitantly where appropriate. When published data indicate that the presence of one complication increases the probability of another complication, the increased probability for the second complication is incorporated into the model as time progresses through the simulation exercise.

The CDM was validated through 66 separate analyses that covered the published studies used to create the model (second order), along with published clinical and epidemiological studies not used in creating the model (third order).\textsuperscript{17} Studies were chosen that described a wide range of diabetic populations, treatments, product delivery settings, and resulting outcomes. Selected studies included the necessary intermediate parameters and were also chosen based on the breadth of coverage for

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**TABLE 1 Characteristics of the Simulated Population Cohorts**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Standard CDM</th>
<th>Customized Obese Cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at start (years)</td>
<td>53 (±10)</td>
<td>53 (±10)</td>
</tr>
<tr>
<td>Duration of diabetes (years)</td>
<td>8 (±5)</td>
<td>8 (±5)</td>
</tr>
<tr>
<td>Female (%)</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>White (%)</td>
<td>81</td>
<td>81</td>
</tr>
<tr>
<td>Black (%)</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Hispanic (%)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Asian/Pacific Islander (%)</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td><strong>Baseline risk factor</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A1c (%)</td>
<td>8.5 (±1)</td>
<td>8.5 (±1)</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>135 (±10)</td>
<td>145 (±10)</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>207 (±30)</td>
<td>217 (±30)</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>41 (±5)</td>
<td>41 (±5)</td>
</tr>
<tr>
<td>LDL-C (mg/dL)</td>
<td>134 (±20)</td>
<td>144 (±20)</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>207 (±30)</td>
<td>230 (±30)</td>
</tr>
<tr>
<td>BMI (Kg/m(^2))</td>
<td>27.5 (±3)</td>
<td>35 (±3)</td>
</tr>
<tr>
<td>Smokers (%)</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Cigarettes/day</td>
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</tr>
<tr>
<td>Alcohol consumption (ounces/week)</td>
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<td>5</td>
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<tr>
<td><strong>Baseline cardiovascular disease complication</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction (%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Angina (%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>PVD (%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Stroke (%)</td>
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</tr>
<tr>
<td>Heart failure (%)</td>
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<td>0</td>
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<tr>
<td>Atrial fibrillation (%)</td>
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<tr>
<td>Left ventricular hypertrophy (%)</td>
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<td>3</td>
</tr>
<tr>
<td><strong>Baseline microvascular complication</strong></td>
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<td></td>
</tr>
<tr>
<td>Microalbuminuria (%)</td>
<td>18</td>
<td>18</td>
</tr>
<tr>
<td>Proteinuria (%)</td>
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<td>2</td>
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<tr>
<td>End stage renal disease (%)</td>
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<td>0</td>
</tr>
<tr>
<td>Diabetic retinopathy (%)</td>
<td>36</td>
<td>36</td>
</tr>
</tbody>
</table>

A1c=glycosylated hemoglobin; BMI=body mass index; BP= blood pressure; CDM= CORE Diabetes Model; HDL-C=high-density lipoprotein cholesterol; LDL-C=low-density lipoprotein cholesterol; PVD=peripheral vascular disease; UKPDS=United Kingdom Prospective Diabetes Study.
specific diabetic complications (e.g., Wisconsin Epidemiological Study of Diabetic Retinopathy for retinopathy outcomes) and time periods (from 1960 to 2003), as clinical treatments and algorithms have evolved significantly over time.

Exenatide Modeling Parameters

To test the hypothesis that weight reduction would improve long-term outcomes in patients treated with exenatide, 2 of the authors (Watkins and Sullivan) used the CDM to compare 2 cohorts of 5,000 type 2 diabetes patients. We began with a hypothetical cohort supplied by the model developer. This group, which we labeled the “standard” cohort and used as a comparison group, was built by the developer using data from the UKPDS study population and had a baseline mean BMI = 27.5 ± 3 kg/m\(^2\). From this template, we built a modified “obese” cohort that had similar demographics, except that mean BMI was 35 ± 3 kg/m\(^2\). Both groups had mean baseline HbA1c levels of 8.5%. Our obese cohort had modestly higher baseline mean blood pressure, total cholesterol, and LDL-C, as would be expected with the much greater body weight. Table 1 shows the baseline input values assigned to each cohort.

The standard cohort was assumed to maintain baseline weight during treatment and the obese group was assumed to experience a mean weight reduction of 3 BMI units, about 15 to 20 pounds (8.5%) in a subject of average adult height, with resulting mean decreases of 10 mm Hg in systolic blood pressure, 20 mg/dL in LDL-C, and 59 mg/dL in triglyceride levels. Corresponding decreases in the nonobese cohort were assumed to be the CDM standard defaults: 1.3 mm Hg in systolic blood pressure, 1.6 mg/dL in LDL-C, and 39 mg/dL in triglyceride levels. All other parameters were identical in both groups, using the defaults supplied with the CDM. It should be noted that all these inputs were either standard values that the CDM model developers have taken from the literature of published diabetes outcome trials or modifications to those values based on published literature. Blonde et al. reported that 314 subjects (57.0% of 551 subjects randomized to exenatide and who completed 82 weeks of therapy) lost an average of 10 pounds (about 5%) over 82 weeks and their mean weight was still decreasing at the end of this period. On this basis, we assumed a long-term mean weight loss of 15 to 20 pounds (8.5%).

In programming our cohort to lose 70% more weight than the 5% mean pounds reported at 82 weeks, we hypothesized that patient selection criteria would include good adherence to dietary as well as medication use instructions. If these individuals continued to maintain a mean weight of 15 to 20 fewer pounds than they would have had without exenatide treatment, we wanted to see what effect this weight loss would have on long-term outcomes predicted by the CDM. These inputs were selected by the payer, in consultation with CORE and with local diabetes experts from whom the payer routinely seeks advice and feedback. None of the input variable assumptions were supplied or influenced by the product manufacturer.

All patients were assumed to be receiving monotherapy with generic metformin at baseline, based on the proposed step-therapy edit recommended by the Premera reviewers on completion of the clinical section of the formulary monograph. This algorithm is also congruent with the advice of local diabetes opinion leaders we consulted and with a recent analysis of Premera diabetes drug use that found that a majority of Premera diabetes patients were currently filling metformin prescriptions.

Recognizing that pharmacy staff at a typical health plan would devote only minimal time to manipulating such a model, we kept the test scenarios simple. In each scenario, 1 additional therapy (active drug or metformin alone [“placebo”]) was added to the treatment groups. We modeled head-to-head comparisons of exenatide versus the following alternative treatments: once-daily insulin glargine, pioglitazone 30 mg, generic glyburide 15 mg, or no additional treatment. (To shorten the text in our tables, the “no additional treatment option” is labeled “placebo.” It should be noted that all the hypothetical patients continued to receive metformin. In this respect, our design resembles an add-on clinical trial.) Drug acquisition costs were based on approximate average ingredient cost per year from actual Premera claims experience from January through December 2005 for all members covered by the plan’s 3-tier formulary. These prices represent the average allowed charge that includes the member cost share and thus represents the payment amounts actually received by pharmacies from the member and the health plan rather than just the amount paid by the plan. The approximate annual costs modeled were exenatide, $2,600; insulin glargine, $1,300; pioglitazone, $2,300; and generic glyburide, $3,000.

We selected a time horizon of 30 years after experimenting with values ranging from 3 to 30 years. We chose 30 years
Because it was the time interval during which the CDM predicted most of the subjects would have died, and the costs obtained thus reasonably project lifetime total direct medical costs for these cohorts. (Figure 1 shows examples typical of the survival curves we saw during this testing.) In these tests, the main difference between the survival curves occurred in the 6-to-30-year range, so this is the time frame in which the CDM is most useful in modeling the chosen population of type 2 patients diagnosed in middle age.

Our model scenario envisioned type 2 diabetics on optimal doses of metformin at baseline who still needed to reduce HbA1c levels by 1 to 2 percentage points (these patients will need at least 1 additional agent added to their metformin regimens). In this situation, the most likely alternatives to adding exenatide would be a sulfonylurea, a thiazolidinedione, or basal insulin. We selected glyburide (identified as “glibenclamide” in the CDM, according to European generic nomenclature), pioglitazone (Actos) and insulin glargine (Lantus) as examples of each of these classes. The CDM calculated projected total treatment costs by organ system, and we used these costs as proxies for severity of cardiovascular, renal, neurological (including sequelae of peripheral neuropathy, such as foot ulcers and limb amputations), and ophthalmic disease. Projected cost of treating hypoglycemia was also reported to the end user in the model outputs.

**Results**

Population characteristics were modeled based on the “UKPDS General” cohort template supplied with the CDM. We cloned and modified this cohort to produce our “Obese Cohort” (mean BMI = 35 ± 3 kg/m²). The resulting demographics and risk factor inputs for our standard and obese cohorts are shown in Table 1.

**Effect on Long-term Disease Burden**

The CDM projected treatment costs for exenatide with metformin, each of the comparator agents with metformin, and no additional treatment (placebo) with metformin. These results are displayed in Table 2. The model predicted an 11% reduction in cardiovascular disease cost with exenatide compared with the alternatives, whereas insulin glargine and
glyburide had more effect on nephropathy and complications of neuropathy.

Cost-effectiveness of Exenatide

Pair-wise comparisons were performed between exenatide and each alternative drug over a 30-year time horizon, assuming continued benefit from treatment with exenatide over this length of time. Exenatide was found to dominate pioglitazone and to be incrementally cost effective (ICER < $50,000/QALY) compared with insulin glargine and no additional treatment, whereas the ICER for glyburide was somewhat higher, reflecting the very low cost of this generic product and its potency in lowering HbA1c. These pair-wise comparisons are summarized in Table 3.

Generally, payers are more interested in short-term rather than long-term treatment costs. Therefore, we examined the effect of time horizon on exenatide incremental cost-effectiveness compared with no additional (metformin only) treatment. The results are displayed in Figure 2. With a 3-year horizon, the predicted ICER was $35,000/QALY gained. This dropped steadily in the 5 to 20-year time frame, when most of these patients would be aged 60 to 75 years, and the complications of diabetes begin to have a major impact on patients’ health and survival. The ICER reached $16,000 per QALY at 20 years and did not further decrease when the calculations were extended to 30 years.

The CDM can also use the projected impact of various treatment interventions to plot survival curves. Figure 1 shows the incremental impact of adding exenatide to patients in our obese cohort compared with continuing metformin monotherapy. The impact of exenatide on survival is small during the first decade of treatment but increases in the second decade, where the difference in percentage of original patients still surviving exceeds 10% for several years.

Discussion

Our modeling scenarios and results were described in the pharmacoeconomic section of the formulary monograph and the key findings included in a slide presentation to the P&T committee members before they voted on the formulary status of exenatide. On the basis of the clinical and pharmacoeconomic evidence gathered, pharmacy staff recommended addition of exenatide to the Premera 3-tier formulary with step-therapy restrictions, requiring prior trial of metformin, consistent with our modeling assumptions and the product label. The P&T committee accepted this recommendation and added to the prior authorization criteria a 1-time review of each patient’s response to exenatide by the prescriber. Documentation of this review will be required before the fourth prescription claim for exenatide is allowed for payment. The P&T committee did not want to specify the magnitude or nature of the patient response, using the logic that it was sufficient to remind prescribers to follow up with the patient, assuming that the physicians would check A1c, assess weight loss and other responses, and adjust therapy as required.

Incomplete clinical data on a new product is a common problem for formulary reviewers, particularly when the drug has a unique mechanism of action. The pressure to be first to market leads manufacturers to design shorter clinical trials when possible and launch the product as quickly as possible. Such trials usually do not provide adequate evidence to predict long-term clinical outcomes without recourse to data from a secondary source. When a product is fast-tracked, even the Phase 3 trials are often pending publication when the initial formulary review by the P&T committee is conducted.

Through use of the AMCP Format, we are asking manufacturers to help us identify responders to their drug, thereby narrowing the target population and improving the predicted NNT and cost-effectiveness. The case of exenatide was particularly enigmatic. It had a novel pharmacologic mechanism that promised improved glycemic control with less risk of hypoglycemia, but no outcome studies existed. Exenatide has been observed to produce modest weight loss in the range of 5% or 5 kg in a population that is otherwise likely to gain weight, especially with tight glycemic control. Some local diabetes opinion leaders were optimistic about the potential benefits of exenatide, but none could articulate how to identify the ideal patient for it.

On the basis of the modest weight loss observed in placebo-controlled phase 3 trials and in a 6-month head-to-head comparison trial of exenatide with insulin glargine, we hypothesized that the likely candidate for exenatide therapy would be obese. If such a patient were able to achieve even a modest weight loss, the long-term effects should be beneficial. The CDM provided a convenient means of testing our hypothesis.

Our modeling supports this hypothesis, though it still does not provide a specific means of identifying responders, especially since most of this population is overweight. Combining our modeling results with the data from clinical trials, we suggest that, until further evidence is available, candidates for exenatide should be obese, in need of further HbA1c reduction at baseline, motivated to lose weight, compliant, willing to self-inject the medication, and able to tolerate significant nausea for the first few weeks of therapy. This rationale was accepted by the P&T committee, but the committee did not impose any of these conditions as criteria for prior authorization.

Time Horizon and Payer Perspective

For reasons previously stated, most of our cost-effectiveness calculations used a 30-year time horizon. It is less necessary to model shorter horizons, since the investigators have already published longitudinal data from open-label extensions of the phase 3 trials to 82 weeks and are continuing to collect these results. It has been argued that employers and payers should be interested in more than a 3-year horizon when optimizing
When one considers the demographics of diabetes, this should resonate with large sophisticated employers since the individuals most likely to suffer increased burden of illness are middle-aged workers in their peak productive years. As improved diabetes therapies continue to be developed, newer drugs may replace exenatide in treatment algorithms, but it is logical that, in the meantime, we should select agents that are likely to produce improved long-term outcomes.

The value of exenatide is very much dependent on the perspective of the payer. Neumann and Sullivan recently commented that the caution of most U.S. payers in adopting cost-effectiveness analyses as a part of health technology assessment is one of the major factors differentiating our health care system from that of other nations with national single-payer systems where the payer’s interests align much better with a societal perspective. They predict that our system will, of necessity, move toward an understanding of value in health that is more like those of other nations, though the change will probably be subtle and incremental and that the AMCP Format will play an important role in this transformation. From society’s viewpoint, a 30-year time frame is of great interest, and we believe that payers should consider longer-term outcomes as well. Health plans have a fiduciary responsibility to purchasers and enrollees to seek the best value for their limited financial resources. For a disease such as diabetes, long-term outcomes must be examined to determine which treatment alternative offers best value for a given patient. Employers interested in productivity and retention of senior staff should take notice, since optimal management of diabetes can delay the development of complications that will reduce employees’ survival (Figure 1) and their work effectiveness later, often during their peak productive years.

However, since U.S. payers traditionally focus on 1- to 3-year time frames corresponding to their budget and contracting cycles, not wishing to ignore their needs, we evaluated the impact of time horizon on the ICER for exenatide versus no additional treatment (see Figure 2). The ICER at 1 year was slightly more than double the 30-year value and still within the limits generally considered to be cost effective. We noted that the exenatide product dossier for U.S. private payers also contains a shorter time horizon budget impact model prepared by CORE at the request of Amylin Pharmaceuticals that projects the expected number of exenatide patients, total drug spending, and per-member-per-month cost for the drug over its first 5 years on the market.

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Limitations

One limitation of this study is that we did not model inhaled insulin (Exubera), the first inhaled insulin product now available in the U.S. market; inhaled insulin may become a popular alternative to other second-line preinsulin medications. Limited clinical data existed at the time of our analysis, and inhaled insulin had not yet been launched; therefore, the pricing was not available. We also did not model liraglutide, a forthcoming competitor with the same pharmacologic mechanism as exenatide. Second, we assumed weight loss with exenatide of 8.5%, considerably more than the approximate 3% in the clinical trials at 30 weeks cited in the product label and the approximate 5% weight loss observed in the open-label observation at week 82 of follow-up for 314 (57.0%) of 551 subjects randomized to exenatide and who completed 82 weeks of therapy.

Third, the decision trees in our models did not take into consideration the cost of switching to alternative therapies, though failure rates of the original treatments based on the literature are taken into consideration in the internal calculations of the CDM. Rather, we assumed that whenever a drug failed, no replacement therapy was tried. This is an oversimplification, since any treatment will always have a certain percentage of failures. While exenatide was well tolerated in the clinical trials, the aggregate dropout rate for adverse events was 4% greater with exenatide treatment than with placebo. Nevertheless, the difference would likely be small enough not to affect the model results, though probably larger than in the trials, where patients would have been coached to manage nausea and other side effects. We noted that the CDM user interface would have allowed us to build complex multibranch treatment decision trees, but none was preprogrammed for us, and we doubt that most payers would take the time to build them from scratch.

Finally, although we did test them to the limits of available data, our informal long-term (30-year) projections would not satisfy the methodological requirements for published pharaco-
economic analyses. The assumption that patients will maintain 3 BMI units (15-20 pounds) weight loss on exenatide for several years is a considerable stretch, since this time horizon extends far beyond the open-label safety extension of the phase 3 trials, from which 82-week data have been published and 2-year data were recently presented. If a more conservative BMI change assumption were entered in the CDM, the ICER results would have increased correspondingly. Also, there was an implicit assumption that no new therapeutic modalities will become available, which is certainly not the case. Also, we assumed that exenatide will at some future date be approved or widely accepted as adjunct therapy with insulin, which may not occur.

We found that, although the modeling results predicted that obese patients would be more likely to benefit from exenatide therapy, the P&T committee chose not to include this criterion in the prior authorization criteria that they approved. This is entirely for practical reasons. Implementing such criteria would require manual review of every request for authorization, because the patient’s weight and BMI are not available to Premera through electronic claims records. Manual verification would require every prescriber to fax information from the patient’s chart to Premera, and neither the plan nor the provider representatives on the committee wanted to take on this extra workload. However, the modeling results still added useful information to the discussion in that we felt more confident that there was a population for whom the drug would be cost effective, even though we did not choose to micromanage the prescribing process.

It is unlikely that most health plans would take the time to learn to use the CDM as it was presented to us. Premera pharmacy staff had to spend 2 hours building scenarios that could have been created for us as defaults, so that we could simply adjust the default assumptions where we felt they were not relevant to our circumstances. The complexity and substance of the CDM are impressive, but those wishing to adapt such models for end use by payers would do well to spend considerable thought and effort designing user interfaces that could be understood by users at varying levels of expertise in pharmacoeconomics. This allows the evaluator to spend most of his/her time thinking about the validity of the clinical inputs and assumptions rather than doing data entry. With a bit of creativity, model builders can design meaningful and intuitive interfaces for novice, intermediate, and advanced end users.

The CDM is only one of several commercially available disease-based diabetes outcome models. Although its complex structure overcomes some of the inherent limitations of Markov modeling, newer object-oriented programs that have recently become available promise a more natural method of simulating the events that would actually occur in a real health care setting, recording patients’ historical experiences and projecting more realistically their impact on future disease progression.

Conclusions

This case illustrates how disease-based economic models could inform the formulary review process by predicting potential reductions in overall cost burden and suggesting subpopulations in which the drug might have greater impact. The AMCP Format is a template for presenting this information to formulary reviewers, a communication tool that facilitates transfer of objective information between the manufacturer and the reviewers who analyze the information for formulary committees. We identified a population that we expected would benefit from a trial of exenatide, but unfortunately, it is not possible to restrict use in others without resorting to a cumbersome, manual prior authorization process, requiring submission of chart data by fax. The P&T committee chose not to impose this administrative burden.

A frequent criticism of manufacturers’ models is that they are inherently biased. While it does not guarantee objectivity, use of a third-party model helps to answer this criticism. The development of modeling standards by organizations such as AMCP and ISPOR provides a framework to judge models somewhat more objectively. Health plans can either develop in-house expertise to perform the evaluations or they can contract with independent third-party pharmacoeconomists. Academic experts capable of performing independent model evaluations may be found in the pharmaceutical outcomes programs offered at many universities around the United States, and most of them are willing to serve as consultants. In addition to evaluating models, academic pharmacoeconomists can teach health plan pharmacists to perform the more straightforward evaluations themselves, if the plan wishes to develop this competency. The Foundation for Managed Care Pharmacy is also a resource for identifying experts in pharmacoeconomic modeling.

Although for practical reasons we did not use the exenatide model for this purpose, application of the model results could assist formulary committees in crafting restrictions to target appropriate patients, reducing NNT, and improving ICERs, especially in institutional settings where patient data such as weight and height are available from electronic medical records. For the manufacturer of a new product, providing a fair and well-constructed model bolsters the case for formulary adoption and helps counter the response that the plan should wait until longer-term clinical data are available before evaluating the product and deciding formulary status.

Finally, AMCP Format dossiers and the economic models within them are communication tools and function best in the context of a relationship between manufacturer and payer in which a certain level of trust has been established. Taking the time to listen carefully and responsively to the payer’s specific needs for information strengthens the relationship and increases the likelihood that the model will receive more than a cursory glance. Since communication is a 2-way process, payers must be willing to take time to meet with the manufacturer’s medical and outcomes liaisons to share their information needs and provide feedback.
Application of Economic Analyses in U.S. Managed Care Formulary Decisions: A Private Payer’s Experience

What is already known about this subject

Long-term outcomes data are rarely available to assist formulary decisions for costly emerging products. Skepticism exists regarding the validity of pharmacoeconomic models generated by drug manufacturers.

What this study adds

Health plans can collaborate with manufacturers to input local assumptions in models that predict cost utility. Careful oversight of assumptions built into the core model is required in addition to review of local inputs to ensure valid output for each MCO.

ACKNOWLEDGMENTS

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DISCLOSURES

No outside funding supported this study. Authors John B. Watkins and Sean D. Sullivan disclose that they are members of the AMCP Format Executive Committee and as such may have some intellectual bias in favor of submitting models. Author Michael E. Minshall discloses that he is an employee of IMS Health, the owner of the CDM model.

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

REFERENCES


There has been a dramatic increase in product approvals in the biotech industry over the past few years. This rapid market expansion is projected to continue for several years due to the proliferation of new specialty drug products and applications to the U.S. Food and Drug Administration (FDA) for additional indications of approved drugs. In 2004, a total of 108 specialty drugs were on the market and another 324 were in development.

Specialty drugs have been the fastest growing segment of drug spending under the pharmacy benefit. The Aon Fall 2005 Health Care Trend Survey indicated that the specialty drug trend rate in 2006 will be 60% higher than the general pharmacy trend rate, with the specialty trend rate forecasted to be 19%, compared with 11.8% for general pharmacy costs. At the current growth rate, it is anticipated that specialty drug spending will double over the next 4 years, accounting for more than 25% of all outpatient pharmacy spending by 2008.

Although less than 3% of the private health care population uses specialty pharmaceuticals, these patients account for 25% to 30% of total medical costs for private health care payers.

Over the last decade, private payers have been intensely focused on managing rising drug costs in general. With new specialty drugs costing anywhere from $10,000 to $200,000 per patient per year, payers will be increasingly faced with significant challenges as new specialty drugs find uses in more common disease states, thus reaching larger populations. Payers will be faced not only with rising costs but also with ethical dilemmas related to which patients can receive these drugs and what the appropriate cost-share will be.

This paper will focus on the most significant challenges facing health care payers with respect to specialty pharmacy management, the solutions payers are implementing, and the potential implications for key stakeholders, including patients, providers, and payers. Examples from the public sector, specifically Medicare Parts B and D, will be included for comparison where they are relevant.

Defining and Categorizing Specialty Drugs
Creating a finite definition for specialty drugs poses a challenge for payers. The terms “biologic,” “biological,” “biopharmaceutical,” and “biotech” are often used interchangeably and imprecisely to describe novel biology-based therapeutics. Not all drugs that are classified as “specialty” are biologic in origin. In general, specialty drugs are defined as high-cost injectable, infused, oral, or inhaled drugs that generally require close supervision and monitoring of the patient’s drug therapy.
Modernization Act (MMA) Final Guidance on Formularies defines a specialty drug as “a Part D drug with plan-negotiated prices that exceed $500 per month.” Table 1 lists the top 10 specialty therapeutic classes, the leading specialty drugs within those classes, and the average annual cost of therapy.

### Traditional Benefit Design Structures

Specialty drugs raise complex cost, access, and administrative issues for payers. They do not fit neatly into traditional benefit design structures in which most prescription drugs are covered under the pharmacy benefit. The result is inconsistency and perhaps inequity among payers in coverage, access, and reimbursement for specialty pharmaceuticals.

Specialty drugs fall into 1 of 2 distinct categories based on the site and method of administration: those that can be administered by either the patient or caregiver, and those that require a health care professional to administer them in a physician's office, infusion center, outpatient hospital department, or home. Survey data indicate that most payers include self-administered injectables (SAIs), such as etanercept (Enbrel) and interferon beta-1a (Avonex), in the pharmacy benefit. There is a large difference in the average monthly cost to a payer for an SAI compared with the cost for other prescription drugs, often more than $1,500 for an SAI compared with an average of $18 per month for generic drugs and an average of $88 per month for brand drugs.

Injectable drugs administered by physicians or other health care providers are commonly termed office-administered injectables (OAI). Most payers include these products under the medical benefit along with physician office procedures, laboratory, radiology, and home health services. Historically, physicians other than oncologists have provided injections to patients in their offices that are relatively low in cost and are administered 1 time only or over a short period, such as antibiotics and anti-inflammatory steroids. In more recent years, physicians other than oncologists have provided OAI that require chronic use, such as natalizumab (Tysabri) and infliximab (Remicade). Oncologists provide supportive care and administer chemotherapy in their offices. In the past, many of the oncology OAI such as intravenous fluorouracil have had a relatively low drug cost, but more recent OAI such as trastuzumab (Herceptin) and bevacizumab (Avastin) are expensive. Most payers today rely on physicians to obtain the OAI drugs, manage the inventory, administer the product, and submit claims for reimbursement for the drugs and professional services. This process is commonly termed “buy and bill.”

### Key Challenges, Payer Strategies, and Potential Implications

Biotechnology therapies present a new set of challenges for the health care system. As most payers depend on the site of administration or the dispensing site to determine the benefit coverage of a drug, the management of these products tends to be “siloed” under either the pharmacy or medical management. Patient cost-share, clinical oversight, utilization management, and provider reimbursement may differ based on the site of

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**TABLE 1** Top 10 Specialty Therapeutic Classes

<table>
<thead>
<tr>
<th>Therapeutic Class</th>
<th>Leading Specialty Drugs – Brand Name</th>
<th>Average Annual Cost of Therapy ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatoid arthritis</td>
<td>Enbrel, Humira, Kineret, Orencia, Remicade, Rituxan</td>
<td>15,000-20,000</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>Avonex, Betsaseron, Copaxone, Rebin, Tysabri</td>
<td>20,000-24,000</td>
</tr>
<tr>
<td>Oral oncology</td>
<td>Gleevec, Tarceva, Nexavar, Revlimid, Sutent, Iressa</td>
<td>40,500-95,000</td>
</tr>
<tr>
<td>Hematopoietics (used as an adjunct to cancer and other therapies)</td>
<td>Procrit, Epogen, Neupogen, Neulasta, Aranesp</td>
<td>5,000-20,000</td>
</tr>
<tr>
<td>Immunosuppressants (used with organ transplants)</td>
<td>Cyclosporine, Cellcept, Zanapax, ATGAM</td>
<td>10,000-45,000</td>
</tr>
<tr>
<td>Human growth hormone</td>
<td>Nutropin, Humatrope, Genotonpin, Nordinpin, tev-Tropin, Satien</td>
<td>18,000-20,000</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>Rebetron, Pegsysys, Peg-Intron, Infergen</td>
<td>24,000-30,000</td>
</tr>
<tr>
<td>Infertility</td>
<td>Follistim, Gonal F</td>
<td>10,000-20,000</td>
</tr>
<tr>
<td>Hemophilia</td>
<td>Recombinant blood factor products</td>
<td>150,000+</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>Forteo</td>
<td>9,000</td>
</tr>
</tbody>
</table>

Adapted from Caremark Trends Rx Report 2006.
administration. Many payers find themselves facing a situation where their ability to manage the use of biotechnology therapy is hampered, in part, because there is no single point of control.

Key challenges in cost and care management of specialty pharmaceuticals arise in the traditional health insurance model from the differences in management and administration of pharmacy and medical benefits, including the following:

- Drug coding systems and integration of pharmacy claims and medical claims data
- Billing systems and payment methods
- Benefit design and patient cost-share
- Clinical and utilization management

Faced with these challenges, payers are eager to develop strategies to manage specialty drugs and are in various stages of strategy development and implementation, using a variety of management tools. As a result, current methods for biotechnology therapy management may not yet provide ideal solutions but represent a starting point for further refinement and improvement.

**Drug Coding Systems and Data Integration**

**Challenges**

Drugs billed under the pharmacy benefit are adjudicated with a National Drug Code (NDC) number, a unique 11-digit number that specifies the drug's manufacturer, strength, dosage form, and package size. The NDC for a new drug is available at the time the drug receives FDA approval and before it enters the market.

Determining the cost of the product is further complicated by the lack of reliable values in the quantity field on medical claims for J codes. A quantity of “1” is common for a J code medical claim, regardless of the actual quantity of the drug administered in metric units.

The use of J codes for medical billing purposes is problematic from another perspective. A J code specific to a drug is assigned anywhere from 6 to 18 months after a drug enters the market. Until a specific J code for a new drug is assigned, a nonspecific code such as J3590 (Unclassified Biologics) or J3490 (Unclassified Drugs) is used for billing, which does not identify the drug being billed. Even 12 to 18 months after initial market introduction and assignment of a specific J code, medical offices may continue to use the nonspecific code (e.g., J3490 or J3590) for a drug with a J code because auditing medical claims for

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**TABLE 2** Partial List of Common Injectable Drugs by Condition* and Site of Administration

<table>
<thead>
<tr>
<th>Condition*</th>
<th>Generic Name</th>
<th>Brand Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatoid arthritis</td>
<td>Etanercept</td>
<td>Enbrel</td>
</tr>
<tr>
<td>Psoriasis</td>
<td>Efalizumab</td>
<td>Raptiva</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>Interferon beta-1a</td>
<td>Avonex</td>
</tr>
<tr>
<td>Incontinence</td>
<td>Cetorexil acetate</td>
<td>Cetrotide</td>
</tr>
<tr>
<td>Infertility</td>
<td>Folitropin beta</td>
<td>Follistim</td>
</tr>
<tr>
<td>Growth disorders</td>
<td>Somatropin</td>
<td>Genotropin</td>
</tr>
<tr>
<td>Hematopoietics</td>
<td>Darbepoetin alpha</td>
<td>Aranesp</td>
</tr>
<tr>
<td>Psoriasis</td>
<td>Alefacept</td>
<td>Amevive</td>
</tr>
<tr>
<td>Respiratory syncytial virus</td>
<td>Palivizumab</td>
<td>Synagis</td>
</tr>
<tr>
<td>Primary pulmonary hypertension</td>
<td>Epoprostenol</td>
<td>Flolan</td>
</tr>
<tr>
<td>Immune disorders</td>
<td>Immune globulin</td>
<td>Baygam</td>
</tr>
<tr>
<td>Other conditions</td>
<td>Interferon gamma-1b</td>
<td>Actimmune</td>
</tr>
<tr>
<td></td>
<td>Botulinum toxin A</td>
<td>Botox</td>
</tr>
<tr>
<td></td>
<td>Imiglucerase</td>
<td>Cerezyme</td>
</tr>
<tr>
<td></td>
<td>Levprolide acetate</td>
<td>Eligard</td>
</tr>
<tr>
<td></td>
<td>Levprolide acetate</td>
<td>Lupron</td>
</tr>
<tr>
<td></td>
<td>Botulinum toxin B</td>
<td>Myobloc</td>
</tr>
<tr>
<td></td>
<td>Omalizumab</td>
<td>Xolair</td>
</tr>
<tr>
<td></td>
<td>Goserelin acetate</td>
<td>Zoladex</td>
</tr>
</tbody>
</table>

*These are U.S. Food and Drug Administration-approved first indications.

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Adapted from the Serono Injectables Digest. 2nd ed. Rockland, MA: Serono; 2006.
accurate and precise use of J codes requires commitment of administrative resources by the payer.

**Payer Strategies**
To fully understand their specialty pharmacy use, payers gather data from pharmacy and medical claims, which often reside in separate databases. For pharmacy claims data, payers can easily identify specialty pharmacy use through the use of query tools dedicated to the pharmacy claims database and the existence of a data field that identifies route of administration. Analysis and evaluation of specialty pharmacy use in medical claims data are more difficult because of several factors such as (a) limited access to the data (e.g., across medical and pharmacy departments), (b) less standardization of medical claims data compared with pharmacy data, and (c) the tendency for payers to capture and enrich pharmacy claims with additional data fields, such as therapeutic class code that does not exist in medical claims data fields.

**Potential Implications**
The lack of a uniform coding system for drugs across pharmacy and medical benefits can result in over- or underpayment to providers and inaccurate accounting of spending on specialty pharmacy drugs. The Department of Health and Human Services recognized this when it proposed the use of NDC numbers for office-administered therapies rather than HCPCS J-codes in the HIPAA (Health Insurance Portability and Accountability Act) Standards for Electronic Transactions. Unfortunately, the original proposal to adopt NDC numbers as the standard for medical data for claims for drugs and biologics was rescinded due to the lack of capacity of current claims and billing systems to accommodate NDC numbers.

**Billing Systems and Payment Methodology**

**Challenges**
Claims billed under the pharmacy benefit are adjudicated in an online real-time electronic payment system based on the NDC number submitted by the pharmacy and are paid at negotiated contract rates. These claims typically undergo sophisticated concurrent clinical review edits, including drug-drug interactions and validation of appropriate dose according to factors such as patient age and gender. Claims billed under the medical benefit are typically batched to the payer and loaded into the payer’s medical claims system with no concurrent clinical review. Contract rates for drugs billed under the medical benefit may vary by provider and are typically higher than pharmacy benefit contract rates. According to recent survey data, the average reimbursement to pharmacies for specialty drugs is average wholesale price (AWP) minus 15%, while the average reimbursement to physician offices for specialty drugs is AWP minus 8%.

As payers have applied cost-management strategies to reimbursement to providers in the pharmacy benefit, J-code reimbursement has been left relatively unchecked. Physicians are often able to bill specialty drugs at a premium well above their acquisition cost, creating a source of profit margin.

Medicare, on the other hand, has more aggressively managed J-code reimbursement for Part B drugs. For example, the physician reimbursement formula was changed to average sales price (ASP) + 6%, effective in January 2005. Beginning January 1, 2006, physicians have had a choice between (1) obtaining these drugs from entities selected to participate in the Competitive Acquisition Program (CAP) in a competitive bidding process, or (2) acquiring and billing for competitively biddable Part B-covered drugs under the ASP drug payment methodology. Individual Medicare plans offering Part D drug benefits negotiate their own rates with network pharmacies, typically reimbursing pharmacies at an AWP discount rate.

**Payer Strategies**
Some payers are managing the actual net cost of specialty drugs by limiting distribution networks and revising reimbursement rates to providers by driving the distribution of specialty drugs through a specialty pharmacy provider (SPP).

SPPs are a diverse group of companies involved in overseeing the distribution, management, and reimbursement of specialty pharmacy products. SPPs have evolved out of several market sectors, including pharmacy benefit managers (PBMs), community pharmacy chains, home infusion companies, disease management companies, and wholesale distributors. PBMs are rapidly taking over the SPP market by either purchasing existing SPPs or creating SPP capabilities from their mail-service facilities.

Industry trends have shown increasing uptake of SPP services, with continued growth expected; 78% of surveyed health plans contract with one or more SPPs or are in the process of contracting with an SPP. Even though payers indicate that they have contracted with one or more SPPs, they do not necessarily require the use of the SPP for all specialty pharmacy products and lock out all other pharmacy providers. Survey data indicate that in 2005, only 48% of payers restricted the distribution of specialty drugs under the pharmacy benefit to contracted SPPs, and only 21% of payers restricted the distribution of specialty drugs under the medical benefit to contracted SPPs. Additionally, some payers will “cherry-pick” selected specialty pharmaceuticals (e.g., therapies for growth hormone, multiple sclerosis, rheumatoid arthritis, and infertility) that they direct to the SPP, based primarily on the drug cost, potential for savings, and opportunities for clinical and utilization management.

**Potential Implications**
The PBM industry’s takeover of the specialty pharmacy industry may inhibit payers from choosing an SPP independent of their PBM. The payer’s choice of vendors can be limited as more PBMs negotiate with their plan sponsors to use the services of
the PBM-SPP exclusively. Also, not all SPPs provide the same level of service nor do they all have the same level of clinical expertise, potentially resulting in different levels of patient care. However, limiting provider access to specialty pharmacy networks may contradict state-specific Any Willing Provider laws, which typically require managed care organizations to contract with any provider that agrees to meet the terms and conditions of the organization.17

Reduced reimbursement to physicians may result in lower overall drug costs. However, as payers restrict physician access and/or reduce their reimbursement rates for specialty pharmaceuticals, there may be indirect repercussions for patients. Some physicians have historically gained significant revenue and gross margin from the “buy and bill” model, where they buy drugs from the vendor of their choice and bill the payer for the drug cost and associated drug administration. When Medicare enacted new pricing methodology in the 2003 MMA, including the option of either ASP + 6% reimbursement or the use of a contracted CAP vendor, oncologists launched an aggressive opposition campaign, noting that the substantially reduced reimbursement might not allow them to continue to provide the same level of service to their patients. The potential loss of revenue from purchasing these drugs may affect the willingness of some physicians to administer these drugs in their offices, and payers are already seeing oncologists shift the administration of less profitable drugs from their office to a hospital outpatient infusion center.18 Payment methods and the amount of gross margin allowed in the reimbursement to physicians may affect patient access and how and where specialty pharmaceuticals are administered; the impact on the quality of care other than patient access requires research.19

Patients are potentially affected both clinically and administratively by reimbursement policy and payment methods. Patients may be affected clinically by potential delay in treatment because nonemergent drugs and biologicals must be ordered from the SPP for each patient rather than selected from the physician office drug inventory. Patients may be affected administratively in that their cost-share obligation may be payable to the SPP rather than to the treating physician.18

**Benefit Design and Patient Cost-Share**

**Challenges**

One of the key components of benefit design is patient cost-share. Cost-share structures usually differ across medical and pharmacy benefits, making it challenging to apply a uniform strategy. Patients typically are assessed a copayment for drugs in the pharmacy benefit, ranging from a monthly average of $10 for a generic drug to a monthly average of $43 for a brand drug.4 On the other hand, managed care plans offer a variety of cost-sharing structures under the medical benefit, ranging from fixed-dollar copayment to 20% coinsurance, with or without an out-of-pocket maximum.1011

**Payer Strategies**

Payers are experimenting with alternative benefit design options for coverage and management of cost and care outcomes for specialty pharmaceuticals. The most commonly discussed coverage strategy is moving all the specialty drugs to the pharmacy benefit.20 Payers are also considering various patient cost-sharing methods for specialty pharmaceuticals such as (a) higher copayment amounts; (b) coinsurance; (c) out-of-pocket payment of maximum dollar amounts per prescription or per year, or both; (d) annual deductibles; and (e) annual benefit maximums in dollar amounts. Survey data from 2005 showed that 11% of health plans have implemented a 4th-tier cost-share for specialty pharmacy products under the pharmacy benefit.21 A typical 4-tier benefit design might have a generic drug copayment of $10, a preferred brand-drug copayment of $25, a nonpreferred brand-drug copayment of $45, and a specialty pharmacy coinsurance in the range of 10% to 25%. To this 4-tier copayment structure can be added features such as a maximum out-of-pocket amount per prescription (e.g., $100) or an annual out-of-pocket maximum, such as $1,500. In a significant departure from the commercial marketplace, approximately 40% of plans offering Medicare Part D drug benefits in 2006 implemented a 4th tier specifically for specialty drugs with an average coinsurance of 25%.22 It is important to note that Part D beneficiaries are automatically limited in their annual out-of-pocket costs as a result of the catastrophic coverage provided in the benefit. Medicare beneficiaries who receive injectable drugs covered under Part B are assessed 20% coinsurance.

**Potential Implications**

Moving all specialty drugs to the pharmacy benefit would result in more uniform application of patient cost-share, clinical management, and utilization management. Including all the specialty drugs under the pharmacy benefit also eliminates some or most of the challenges in drug coding, data integration, billing, and payment that were identified earlier. On the other hand, patients who previously had little if any cost-share responsibility for drugs received under the medical benefit may be assessed a copayment or coinsurance, whereas patients who did have coinsurance for their medical benefit drugs may find their cost-share to be either higher or lower for specialty pharmaceuticals adjudicated under the pharmacy benefit.

There may be other plan-specific operational challenges that interfere with a payer’s ability to move all injectable drugs to the pharmacy benefit. While management of all specialty drugs under the pharmacy benefit might be advantageous from the payer perspective, contract arrangements with providers—physicians and pharmacies—would be affected. Physicians would either need the capability to submit claims directly to the pharmacy (a process not currently supported by most medical office management systems) or rely on the contracted SPP to drop-ship the medication and bill the health plan directly,
resulting in a need for modification of physician reimbursement for services and potential lost revenue to the physician from “buy and bill.” Additionally, payers would need to accommodate employer groups who had either carved out their pharmacy benefits to a PBM or who had chosen not to offer a pharmacy benefit at all.

Some observers have expressed concern that higher patient cost share may adversely affect compliance with drug therapy, including the increased likelihood of skipped doses. The RAND Health Insurance Experiment demonstrated that when people have to pay for more of their care out of their own pockets, they use fewer medical services, including standard prescription benefits. Alternatively, a more recent study conducted by RAND researchers examined the elasticity of specialty drug demand and found that increased cost-sharing for specialty products does not reduce the use of these products but only transfers a much larger financial burden from the health plan to the patient. Insufficient data exist on the impact of cost sharing for biologics on overall patient adherence and long-term persistence with therapy. It is possible that any cost-share amount, even relatively small, can adversely affect patient adherence. Research will be necessary from a population perspective to determine the optimum balance between the amount of the member cost-share and patient adherence to those specialty pharmaceuticals that are determined to have high value in clinical outcomes.

**Clinical and Utilization Management**

**Challenges**

For specialty pharmaceuticals covered under the pharmacy benefit, most payers have turned to the traditional techniques employed by PBMs for managing the benefit for conventional drugs, including step therapy, quantity limits, prior authorization, and drug utilization review. Conversely, for many payers, very little cost or care management exists for specialty pharmaceuticals covered under the medical benefit. In some cases, payers have implemented prior authorization programs to review some of these therapies to ensure “appropriate use” as defined by FDA labeling and evidence-based clinical guidelines. In some circumstances, payers may only cover a drug according to its FDA-approved labeled indication; however, state law may mandate coverage of off-label use if there is sufficient evidence for use as cited by one or more national compendia. For example, the Association of Community Cancer Centers (ACCC) spearheaded efforts to make citation of a cancer drug in any of the standard reference compendia sufficient to require insurers to pay for its use outside of FDA-approved label indications. As of January 2006, 39 states have passed legislation regarding off-label drug use that follows the ACCC recommendation.

However, these restrictions on use are difficult to implement and administer under the medical benefit because claims are submitted after a service has been administered, not in real-time electronic format, and the staff responsible for medical management is typically not sufficiently trained in drug utilization management. As a result, drugs in the same therapy class may have different clinical management criteria applied to them, depending on the site of care and the billing provider. For example, a pharmacy claim submitted for etanercept (injection) to treat a patient with rheumatoid arthritis may be reviewed, either manually or electronically, for prior use of an appropriate oral therapeutic agent such as methotrexate (i.e., step therapy), whereas a medical benefit claim for infliximab (intravenous infusion) is unlikely to be reviewed for adherence to step therapy and may not be reviewed for use in an FDA-approved indication.

**Payer Strategies**

Payers recognize that developing an effective specialty pharmacy program involves much more than simply providing access to drugs at a discounted rate. Specialty pharmacy programs also typically focus on the development of clinical protocols, utilization management, and quality of care standards. Payers may use their existing pharmacy and therapeutics (P&T) committee, medical policy committee, technology assessment committee, or outside services to develop coverage guidelines. Some organizations have developed new committees to review specialty pharmacy drugs and technology. For example, Kaiser Permanente California has created a formal, centralized multidisciplinary group—the Biotechnology and Emerging Pharmaceutical Technology Assessment Committee—to review biotech drugs before review by their P&T committee. There are often special considerations related to the clinical review of specialty drugs. Because of the FDA’s accelerated process for certain classes of drugs, some have been approved without evidence produced in published randomized clinical trials. Therefore, payers in these cases have been forced to create clinical coverage guidelines in the absence of evidence of effectiveness. Other specialty pharmaceutical classes, such as drugs for rheumatoid arthritis, multiple sclerosis, or hepatitis C virus (HCV), have more evidence to support the development of coverage criteria and utilization management criteria.

Payers are also selecting preferred products in some drug classes and disease states where there are multiple therapy options within the class, including therapies to treat rheumatoid arthritis, multiple sclerosis, HCV, and growth hormone deficiency. Payers may have the ability to steer use to particular products to receive market share rebates from drug manufacturers. According to a survey, 45% of payers in 2004 had preferred products in at least 1 specialty pharmacy therapeutic category.

Due to the complex nature of most of these specialty pharmacy therapies, patients require care management to achieve optimal outcomes. Many health plans and employers have turned to SPPs to not only distribute specialty drugs but also to provide clinical services, including side-effect management, proactive
Specialty Pharmacy Cost Management Strategies of Private Health Care Payers

Potential Implications

At the time of market availability of a new specialty pharmaceutical, there may be minimal evidence available for decision making regarding coverage and utilization management. Pharmacoeconomic modeling may help inform decision makers about the impact on pharmacy budgets until more information becomes available on the actual effects on direct and indirect costs and clinical outcomes, and these results can be factored into clinical guidelines. Some health plans have adopted The AMCP Format for Formulary Submissions (Academy of Managed Care Pharmacy) and require pharmaceutical and biotechnology companies to submit dossiers for specialty drugs. As therapeutic categories become more mature and there are more products within the categories, nationally recognized evidence-based guidelines may become available that can be adopted by payers. For example, the American Academy of Pediatrics developed a guideline for respiratory syncytial virus, and the National Institutes of Health developed guidelines for the treatment of HCV. At year-end 2006, there are only a handful of cost-effectiveness analyses for high-cost new technology pharmaceuticals, primarily for anti-TNF (tissue necrosis factor) agents (etanercept, infliximab, adalimumab, and anakinra) for the treatment of rheumatoid arthritis. For now, payers are making decisions on the basis of data that are available to them from many disparate sources and are making the best of a situation rife with fragmented information.

The selection of preferred products within therapeutic categories needs to take into account the mechanism of action of each agent; it cannot be assumed that all biologics that are indicated to treat a specific disease are equivalent without head-to-head studies to confirm this activity. Additionally, as the medical community becomes more comfortable with these drugs, there will be more off-label use, making it more difficult to select preferred products if each drug has a number of clinical applications. Payers at this time have typically been open-minded about off-label use of biologics and other specialty pharmaceuticals. Under the Medicare Part D benefit, Medicare will only authorize off-label use if it is cited in 1 of the 3 approved drug compendia listed in the MMA. It remains to be seen if payers will become more aggressive in their management of off-label drug use and to what extent certain states will impose mandates for coverage of off-label uses. Table 3 lists selected common off-label uses of biologics.

Delegating the role of clinical and utilization management to an SPP needs oversight because these vendors are typically contracted on a fee-for-service basis and receive revenue from the sale of drugs and from administrative fees for claim transactions. The result may be unaligned incentives, in which the

**Table 3**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Approved Indications</th>
<th>Unapproved Uses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adalimumab (Humira)</td>
<td>Rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis</td>
<td>Psoriasis, ulcerative colitis</td>
</tr>
<tr>
<td>Beclomethasone (Regranex)</td>
<td>Diabetic foot ulcers, wound care</td>
<td>Venous leg ulcers, scleroderma, sickle cell disease</td>
</tr>
<tr>
<td>Bevacizumab (Avastin)</td>
<td>Metastatic colorectal cancer, non-small cell lung cancer</td>
<td>Wet age-related macular degeneration, late-stages breast cancer, lung cancer, kidney cancer</td>
</tr>
<tr>
<td>Cisplatin (Platinol)</td>
<td>Bladder, testicular, ovarian cancer</td>
<td>Thyroid and lung cancers</td>
</tr>
<tr>
<td>Eladertzumab (Raptiva)</td>
<td>Psoriasis</td>
<td>Granuloma annulare</td>
</tr>
<tr>
<td>Etanercept (Enbrel)</td>
<td>Psoriasis, psoriatic arthritis, rheumatoid arthritis, ankylosing spondylitis, osteoarthritis</td>
<td>Behcet’s disease, sarcoidosis, wound ulcers, vasculitides, pyoderma gangrenosum</td>
</tr>
<tr>
<td>Ibritumomab tiuxetan (Zevalin)</td>
<td>Non-Hodgkin’s lymphoma</td>
<td>Various cancers</td>
</tr>
<tr>
<td>Infliximab (Remicade)</td>
<td>Rheumatoid arthritis, psoriatic arthritis, ulcerative colitis, Crohn’s disease, ankylosing spondylitis, psoriasis</td>
<td>Kawasaki’s disease, Sjogren’s syndrome</td>
</tr>
<tr>
<td>Oxaliplatin (Eloxatin)</td>
<td>Metastatic colon cancer, pancreatic cancer</td>
<td>Postsurgery drug regimens, newly diagnosed colorectal cancer</td>
</tr>
<tr>
<td>Rituximab (Rituxan)</td>
<td>Non-Hodgkin’s lymphoma, rheumatoid arthritis</td>
<td>Skin malignancies, blood cancers</td>
</tr>
<tr>
<td>Sunitinib (Sutent)</td>
<td>Gastrointestinal stromal tumors, advanced kidney cancer</td>
<td>Breast, colon, and pancreatic cancers (in clinical trials)</td>
</tr>
<tr>
<td>Trastuzumab (Herceptin)</td>
<td>Metastatic breast cancer</td>
<td>Early-stage breast cancer</td>
</tr>
</tbody>
</table>

Defining the Value of Specialty Pharmacy

At the core of the debate around specialty pharmaceuticals is the question of value. Is the drug worth it? Is the higher additional cost of the drug offset by significantly better patient outcomes or by avoiding other longer-term costs? Even though “value” is the focus of the managed care industry, few payers have the information necessary to define the value of specific specialty pharmacy therapies. The AMCP Format for Formulary Submissions defines value in this way: “Value in health care relates to whether a medical intervention . . . improves health outcomes enough to justify the additional dollars spent compared to another intervention.” A conundrum can be created by patient demand for new products that may appear to be therapeutic breakthroughs but for which outcomes data are lacking. One practical result is that payers will often experience difficulty in denying payment for treatment. Additionally, coverage policy in health plans has not traditionally been designed to evaluate the therapeutic value of particular treatments relative to their direct or indirect cost. Payers are looking increasingly to the pharmaceutical industry and specialty pharmacies to demonstrate the clinical and economic value of new specialty therapies and related support services. However, it is not yet certain that the pharmaceutical industry or specialty pharmacies will have sufficient motivation and commitment to produce the evidence-based evaluations that are necessary to inform payers of the value of specialty pharmacy products and services.

The primary tool currently used by SPPs to demonstrate positive clinical outcomes is the measurement of adherence to therapy. A high rate of adherence with specialty drug regimens is often critical to both short- and long-term outcomes. For example, adherence to therapy of greater than 80% has been linked directly to positive treatment outcomes for patients with HCV. SPPs have been able to document improved adherence to therapy for patients using their services compared with a control group that received their medication through community pharmacies; however, only a few SPPs have actually published their results, and thus far only as poster abstracts. While specialty pharmacies promote the fact that they are able to demonstrate value to their customers, there is a lack of published, peer-reviewed studies indicating their effectiveness in improving health outcomes and reducing overall health care costs. As a result, research is needed to determine the value of SPPs by the measures of clinical, service, and cost outcomes.

Conclusions

While specialty pharmacy therapies continue to bring promise of medical and clinical innovations to patients with debilitating chronic diseases, they also pose challenges to the payers who are faced with decisions regarding their coverage, reimbursement, clinical management, and access. The high direct cost of most specialty pharmaceuticals has precipitated the need to reconsider the structure of pharmacy and medical benefits in health plans. Innovative thinking is still necessary to address the current and future challenges posed by specialty pharmaceuticals. Clinical, service, and cost outcomes of specialty pharmacy products will become increasingly important in health care. Overall, there is an emergent need to evaluate outcomes as high-cost specialty pharmaceuticals expand from use in niche areas such as orphan diseases (e.g., tissue-specific cancer) to larger populations with broader indications, such as asthma and diabetes.

Not all strategies employed by payers today are optimal and generally represent a stop-gap approach for controlling rising drug costs. Yet, the need for vigilant management of these high-cost therapies appears obvious, and much more outcomes data are necessary to inform decision makers responsible for determining coverage and managed care interventions for specialty pharmaceuticals.

What is already known about this subject

Most managed care payers have a broad knowledge of the various challenges related to the management of specialty pharmaceuticals and are familiar with most of the drugs included in this category.

What this study adds

This study outlines some of the methods to manage specialty pharmaceuticals, some of the challenges to effective cost and care management of these agents, and some of the potential implications for policy development by public and private payers.

DISCLOSURES

No outside funding supported this study. Author Debbie Stern served as principal author of the study. Study concept and design, data collection and interpretation, and writing of the manuscript and its revision were primarily contributed by Stern, with input from author Debi Reissman. The authors disclose no potential bias or conflict of interest relating to this article.

REFERENCES/NOTES

5. In the context of this article, “private health care payers” includes health plans, employers that purchase health care coverage through health plans, and employers that insure their own health care costs and are noted collectively in the text as “payers.”

6. As consultants involved in managed care pharmacy, the authors are exposed to various payer strategies. Sources of general market intelligence include market research interviews, focus groups, and direct consulting with health plans, PBMs, employers, and specialty pharmacies.


RESULTS: For the physician practice assessment portion of the project, we used patient charts if there was a complete (total cholesterol, TG, HDL-C, LDL-C) lipid profile for baseline and follow-up, and a minimum of 6 weeks between baseline and follow-up values. At follow-up, the proportion of patients meeting goal lipid values according to the guidelines for LDL-C was 68%, 63% for HDL-C, 59% for TG, and 68% for non-HDL-C. Only 32% of patients met all 3 goals (LDL-C, HDL-C, and TG). The average time between the baseline and follow-up lipid profile was 3.7 years, with a median of 2.9 years, and a minimum of 6 weeks and a maximum of 42 years. Compared with baseline, the most recent follow-up lipid assessment for LDL-C goal attainment showed improvement by an absolute 6%, from 57% to 63% of patients. TG goal attainment improved an absolute 18% (from 41% to 59%), LDL-C goal attainment improved an absolute 45% (from 23% to 68%), non-HDL-C goal attainment improved an absolute 46% (from 22% to 68%), and the combined goals of LDL-C, HDL-C, and TG improved from 8% of patients at baseline to 32% at follow-up. Of the 2,119 patients in the study population, 1,784 (84%) at the time of chart review had been prescribed at least 1 lipid-modifying medication; 1,552 (87%) a single lipid-modifying medication and 232 (13%) combination therapy. The hydroxymethylglutaryl (HMG) coenzyme-A reductase class (statins) accounted for 89% of the monotherapy regimens. Of the patients with baseline LDL-C, HDL-C, and TG readings, 40% could have been diagnosed as having mixed hyperlipidemia, defined as having (a) baseline LDL-C greater than their NCEP ATP III goal and (b) either baseline TG of >150 mg/dL or a baseline HDL-C of <40mg/dL for males or <50 mg/dL for females. Of the 40% of patients estimated to have mixed hyperlipidemia, 69% were prescribed lipid-modifying monotherapy, 18% were prescribed combination drug therapy, and 14% were not prescribed drug therapy.

CONCLUSION: Attainment of therapeutic goals for serum lipids improved from baseline to follow-up, but approximately one third of patients did not achieve individual lipid goals and two thirds of patients did not attain goal for all 3 targets (LDL-C, HDL-C, and TG).

KEYWORDS: Hyperlipidemia, Hypercholesterolemia, Mixed hyperlipidemia, Dyslipidemia, Statin, Coronary heart disease

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C oronary heart disease (CHD) affects an estimated 13 million Americans and is the leading cause of death in both males and females in the United States. About every 26 seconds, an American will suffer a coronary event and about every minute, someone will die from a coronary event. In 2006, the estimated direct and indirect costs of CHD in the United States are estimated to be $142.5 billion.1

Given the high incidence, prevalence, and economic burden of CHD, prevention strategies are of crucial importance. Independent, modifiable risk factors for CHD are numerous, and include hypertension, smoking, obesity, physical inactivity, and abnormal serum lipids.2,3 Among lipids, elevated low-density lipoprotein cholesterol (LDL-C), low-density lipoprotein

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Authors

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Total Therapeutic Management, a disease management and health care research organization, was engaged by the sponsor of this study to examine the real-world therapeutic management of elevated LDL-C, HDL-C, TG, and non-HDL-C levels individually and in combination (mixed hyperlipidemia) against NCEP ATP III and AHA guidelines in patients diagnosed with hyperlipidemia and/or hypercholesterolemia (Table 1). The sponsor was also interested in the proportion of patients who did not have a diagnosis or diagnosis code for mixed hyperlipidemia but who might be classified more accurately as having mixed hyperlipidemia.

Review by an institutional review board was not sought for this study since the abstracted data delivered to the authors were deidentified with no opportunity to trace the data back to individual patients.

### Methods

A total of 600 of the highest-volume prescribers of lipid-modifying drugs, 100 each from 6 metropolitan service areas (Atlanta, Georgia; Cleveland, Ohio; Milwaukee, Wisconsin; New York, New York; San Francisco, California; and Seattle, Washington) were identified from the IMS Health prescription database (Table 2). Each provider was given 6 months to return the completed 25 patient data abstraction forms. In total, 103 prescribers (17 from Atlanta, 20 from Cleveland, 20 from Milwaukee, 13 from New York, 15 from San Francisco, and 18 from Seattle) agreed to participate, had at least 25 patients meeting the inclusion criteria, and returned their completed data abstraction forms in the required timeframe. In return, each provider received feedback on the comparison of their practice with other practices and national guidelines. No compensation was provided to the participating prescribers or to their office staff. Two prescribers in the New York metropolitan area did not have complete baseline and follow-up lipid profiles for their patients and were excluded from the results, leaving 101 physician practices (Table 2), approximately 17% of original samples.

The prescribers were asked to identify, by *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) billing codes, all patients aged between 18 and 79 years who were seen in their practice in the last 2 years having a diagnosis of hyperlipidemia (ICD-9-CM code 272.4) and/or hypercholesterolemia (ICD-9-CM code 272.0). ICD-9-CM code 272.2 (mixed hyperlipidemia) was purposely excluded from the criteria for patient chart selection to permit estimation of the proportion of patients who did not have a diagnosis or diagnosis code for mixed hyperlipidemia but who might be classified more accurately as having mixed hyperlipidemia.

On the basis of the number of patients identified by each practice meeting the aforementioned criteria, we developed a random number list using SAS v8.2 statistical software (SAS Institute, Inc., Cary, NC). We then ranked the identified patients alphabetically by last name and numbered sequentially for each physician practice. Using the random number list specific to that physician practice, we selected 25 patients for medical record review. Of the total 2,525 patient charts from 101 physician practices, 406 (16%) had an incomplete lipid profile for baseline and follow-up or more than 6 weeks between baseline and follow-up lipid values; therefore, the sample size for analysis was 2,119 patients (Table 2).

One staff member from each physician practice reviewed

### Table 1

<table>
<thead>
<tr>
<th>CHD Risk Factors, Risk Equivalents, and Optimal Lipid Values Based on NCEP ATP III and AHA Guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CHD Risk Factors</strong></td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Cigarette smoking</td>
</tr>
<tr>
<td>Low HDL-C (&lt;40 mg/dL)</td>
</tr>
<tr>
<td>Family history of premature CHD</td>
</tr>
<tr>
<td>Age (men ≥45, women ≥55 years)</td>
</tr>
<tr>
<td><strong>Lipid Fraction</strong></td>
</tr>
<tr>
<td>LDL-C</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>HDL-C</td>
</tr>
<tr>
<td></td>
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<tr>
<td></td>
</tr>
<tr>
<td>TG</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

* Intermediate risk is defined as having ≥2 CHD risk factors, per NCEP ATP III.
† Low risk is defined as having <2 CHD risk factors, per NCEP ATP III.
‡ Calculated value (total cholesterol minus HDL-C), per NCEP ATP III guidelines.
§ AHA recommendation.
AHA = American Heart Association; CHD = coronary heart disease; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; NCEP ATP III = National Cholesterol Education Program Adult Treatment Panel Third Report; TG = triglyceride.
these medical records using a standardized data collection form. The data abstractor from each physician practice received uniform verbal and written directions on how to complete the data collection form. This data collection form was designed to gather information on patient demographics, clinical history, comorbid disease states, laboratory test results (total cholesterol, LDL-C, HDL-C, TG, and liver function tests) and cholesterol drug therapy pertinent to the management of dyslipidemia. Non-HDL-C was calculated from the difference between total cholesterol and the HDL-C value. Patient inclusion criteria required new starts to cholesterol drug therapy or at least a 6-week washout period from previous cholesterol medications before starting current cholesterol medications. Also, baseline lipid values were recorded at least 6 weeks before the initiation of cholesterol drug therapy or 6 weeks free of cholesterol drug therapy, whichever was more recent. Follow-up values were the most recent lab values from the date of data abstraction but at least 6 weeks after baseline. Data abstraction occurred in physician offices from March 2004 through August 2004.

The medical record for each patient was reviewed to determine individual goal values for LDL-C, non-HDL-C, and TG based on the NCEP ATP III guidelines. Goal HDL-C was determined from the NCEP ATP III (men) or AHA (women) guidelines. The NCEP ATP III guidelines were chosen for men because they are the most widely publicized and used cholesterol management guidelines, and the AHA guidelines were chosen for women because they are the most specific for women. The appropriate

| TABLE 2 | Derivation of Sample of Patient Charts* and Patients With Recorded Lipid Values |
| Inclusion criteria | Age 18-79 years |
| Exclusion criteria | Prescribers deny request to participate |
| Top 100 providers identified in metropolitan areas | 600 prescribers identified (100 in each metropolitan area) |
| Prescribers volunteering to participate in study | 120 providers enrolled; 103 providers returned data |

<table>
<thead>
<tr>
<th>City</th>
<th>Data collected (N)</th>
<th>Included for analyses (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atlanta</td>
<td>17</td>
<td>17</td>
</tr>
<tr>
<td>Cleveland</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Milwaukee</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>New York</td>
<td>13</td>
<td>11</td>
</tr>
<tr>
<td>San Francisco</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Seattle</td>
<td>18</td>
<td>18</td>
</tr>
<tr>
<td>Total number of prescribers participating</td>
<td>103</td>
<td>101</td>
</tr>
<tr>
<td>Total number of patient charts</td>
<td>2,570†</td>
<td>2,119‡</td>
</tr>
</tbody>
</table>

* Patient charts were abstracted during the period from March 2004 through August 2004. The length of time between baseline lipid values and follow-up was between 6 weeks and 42 years.
† Five charts were incomplete (2,575 - 5 = 2,570).
‡ Two providers (50 patients) and 401 patients from other providers were excluded for not providing complete baseline and follow-up lipid profiles on their patients.

| TABLE 3 | Study Population Characteristics (N=2,119) |
| Characteristic | N (%) |
| Primary prevention* | 1,668 (79) |
| Secondary prevention† | 451 (21) |
| Hypertension | 1,264 (60) |
| Metabolic syndrome‡ | 741 (35) |
| Obesity (chart documented) | 684 (32) |
| Diabetes mellitus | 570 (27) |
| Coronary heart disease (CHD)§ | 398 (19) |
| Family history of early CHD | 333 (16) |
| Current smoker | 202 (10) |
| Stroke/TIA | 73 (3) |

* Primary prevention=those patients who did not have a notation in the chart of CHD, or stroke, or TIA; CHD was defined as a specific notation in the chart of at least 1 of these terms: CHD, angina, MI, angina plasty, or coronary artery bypass surgery.
† Secondary prevention=those patients who had CHD or stroke/TIA.
‡ Metabolic syndrome was defined as having ≥2 characteristics (abdominal obesity [male and waist circumference ≥40 inches, female and waist circumference ≥35 inches, or chart documented obesity], triglycerides ≥149mg/dL, HDL-C <40 mg/dL for males or 50 mg/dL for females, hypertension, or diabetes mellitus).
§ Chart notation of 1 or more of the following terms: CHD, MI, angina, angioplasty, or bypass surgery.
MI=myocardial infarction; TIA=transient ischemic attack.
Results of Retrospective Chart Review to Determine Improvement in Lipid Goal Attainment in Patients Treated by High-Volume Prescribers of lipid-Modifying Drugs

optimal values were determined by assessing the presence of CHD, CHD risk factors, and CHD risk equivalents. CHD was defined as a notation in the patient chart of CHD, myocardial infarction (MI), angina, angioplasty, or bypass surgery. The definition of risk factors and risk equivalents along with definitions of optimal values for LDL-C, HDL-C, non-HDL-C, and TG used in this study are presented in Table 1.

All collected data were aggregated and analyzed, and a report using charts and graphs was developed for each prescriber’s practice. Data analysis was performed using SAS v8.2 statistical software. We performed analysis for the overall patient population and for subgroups including males, females, patients ≥65 years, CHD, diabetes mellitus, metabolic syndrome, and peripheral arterial disease.

Results

Among the 101 physician prescribers participating in this analysis, 82% were primary care physicians (family practice, internal medicine, or general practice), 8% were endocrinologists, 6% were cardiologists, 1% were nephrologists, and 3% were classified as other specialty.

Of the 2,119 patients included in this study, the vast majority, 79% (1,668/2,119), were treated for primary prevention; 55% (n = 1,158) were male, 44% (n = 945) were female, and 1% (n = 16) of the population had no gender documented in their medical chart (Table 4). The mean age and standard deviation at the time of data collection was 61 ±12 years.

Lipid values for the overall population, by gender and by age ≥65 years, are summarized in Table 4. Baseline was defined as

### TABLE 4 Baseline and Follow-up Lipid Values (N = 2,119)

<table>
<thead>
<tr>
<th>Lipid Fraction</th>
<th>All Patients at Baseline</th>
<th>All Patients at Follow-up</th>
<th>Males* at Baseline</th>
<th>Males* at Follow-up</th>
<th>Females* at Baseline</th>
<th>Females* at Follow-up</th>
<th>Age ≥65 at Baseline</th>
<th>Age ≥65 at Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>2,119</td>
<td>2,119</td>
<td>1,158</td>
<td>1,158</td>
<td>945</td>
<td>945</td>
<td>822</td>
<td>822</td>
</tr>
<tr>
<td>Total cholesterol mg/dL†</td>
<td>2,119</td>
<td>2,119</td>
<td>1,158</td>
<td>1,158</td>
<td>945</td>
<td>945</td>
<td>822</td>
<td>822</td>
</tr>
<tr>
<td>N</td>
<td>2,119</td>
<td>2,119</td>
<td>1,158</td>
<td>1,158</td>
<td>945</td>
<td>945</td>
<td>822</td>
<td>822</td>
</tr>
<tr>
<td>Mean</td>
<td>238.8</td>
<td>188.7</td>
<td>233.4</td>
<td>181.7</td>
<td>245.7</td>
<td>197.3</td>
<td>236.6</td>
<td>184.9</td>
</tr>
<tr>
<td>± SD</td>
<td>±45.9</td>
<td>±41.2</td>
<td>±46.9</td>
<td>±37.7</td>
<td>±43.6</td>
<td>±43.2</td>
<td>±45.1</td>
<td>±43.7</td>
</tr>
<tr>
<td>Median</td>
<td>237.0</td>
<td>183.0</td>
<td>233.0</td>
<td>177.0</td>
<td>244.0</td>
<td>190.0</td>
<td>237.0</td>
<td>178.0</td>
</tr>
<tr>
<td>LDL-C mg/dL</td>
<td>N</td>
<td>1,941</td>
<td>2,061</td>
<td>1,040</td>
<td>1,122</td>
<td>886</td>
<td>923</td>
<td>775</td>
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<tr>
<td>Mean</td>
<td>152.6</td>
<td>108.4</td>
<td>150.6</td>
<td>105.9</td>
<td>154.9</td>
<td>111.3</td>
<td>149.6</td>
<td>103.0</td>
</tr>
<tr>
<td>± SD</td>
<td>±39.8</td>
<td>±34.2</td>
<td>±40.9</td>
<td>±32.7</td>
<td>±38.4</td>
<td>±35.6</td>
<td>±39.5</td>
<td>±33.9</td>
</tr>
<tr>
<td>Median</td>
<td>154.0</td>
<td>103.0</td>
<td>152.0</td>
<td>102.5</td>
<td>156.0</td>
<td>104.0</td>
<td>150.0</td>
<td>98.0</td>
</tr>
<tr>
<td>HDL-C mg/dL</td>
<td>N</td>
<td>2,119</td>
<td>2,119</td>
<td>1,158</td>
<td>1,158</td>
<td>945</td>
<td>945</td>
<td>822</td>
</tr>
<tr>
<td>Mean</td>
<td>48.2</td>
<td>49.6</td>
<td>43.8</td>
<td>45.0</td>
<td>53.5</td>
<td>55.1</td>
<td>49.7</td>
<td>51.2</td>
</tr>
<tr>
<td>± SD</td>
<td>±17.3</td>
<td>±14.6</td>
<td>±17.5</td>
<td>±12.9</td>
<td>±15.6</td>
<td>±14.7</td>
<td>±17.2</td>
<td>±14.8</td>
</tr>
<tr>
<td>Median</td>
<td>46.0</td>
<td>47.0</td>
<td>41.0</td>
<td>43.0</td>
<td>51.0</td>
<td>53.0</td>
<td>48.0</td>
<td>49.0</td>
</tr>
<tr>
<td>TG mg/dL</td>
<td>N</td>
<td>2,119</td>
<td>2,119</td>
<td>1,158</td>
<td>1,158</td>
<td>945</td>
<td>945</td>
<td>822</td>
</tr>
<tr>
<td>Mean</td>
<td>219.7</td>
<td>157.8</td>
<td>230.2</td>
<td>160.1</td>
<td>206.8</td>
<td>155.2</td>
<td>203.7</td>
<td>154.0</td>
</tr>
<tr>
<td>± SD</td>
<td>±230.7</td>
<td>±105.5</td>
<td>±254.5</td>
<td>±112.0</td>
<td>±197.2</td>
<td>±97.5</td>
<td>±187.7</td>
<td>±98.8</td>
</tr>
<tr>
<td>Median</td>
<td>171.0</td>
<td>134.0</td>
<td>173.0</td>
<td>135.0</td>
<td>167.0</td>
<td>132.0</td>
<td>168.0</td>
<td>132.0</td>
</tr>
<tr>
<td>Non-HDL-C mg/dL</td>
<td>N</td>
<td>2,119</td>
<td>2,119</td>
<td>1,158</td>
<td>1,158</td>
<td>945</td>
<td>945</td>
<td>822</td>
</tr>
<tr>
<td>Mean</td>
<td>190.6</td>
<td>139.1</td>
<td>189.6</td>
<td>136.7</td>
<td>192.2</td>
<td>142.2</td>
<td>186.8</td>
<td>133.7</td>
</tr>
<tr>
<td>± SD</td>
<td>±45.9</td>
<td>±40.1</td>
<td>±47.2</td>
<td>±37.8</td>
<td>±44.1</td>
<td>±42.4</td>
<td>±45.4</td>
<td>±42.2</td>
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<tr>
<td>Median</td>
<td>188.0</td>
<td>134.0</td>
<td>188.0</td>
<td>133.0</td>
<td>190.0</td>
<td>134.0</td>
<td>187.0</td>
<td>127.0</td>
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* Gender was not recorded in 16 charts.
† Total cholesterol was recorded to permit calculation of non-HDL-C (total cholesterol minus HDL-C).
HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; TG = triglyceride.
at least 6 weeks before prescribing or free of any lipid-modifying medication therapy for 6 weeks. The median baseline LDL-C, HDL-C, TG, and non-HDL-C values for the overall population were 154 mg/dL for LDL-C, 46 mg/dL for HDL-C, 171 mg/dL for TG, and 188 g/dL for non-HDL-C. Non-HDL-C was calculated by subtracting the HDL value from the total cholesterol value.\(^a\)

The distribution of baseline pharmacotherapy for cholesterol disorders is summarized in Table 5. A total of 335 patients (16%) received no drug therapy. Of the 1,784 patients who were prescribed lipid-modifying medication therapy, 1,552 (87%) were prescribed monotherapy and 232 patients (13%) were prescribed combination therapy. The proportion of the different lipid-modifying medications as monotherapy and as combinations was relatively the same across each category. Statins were the most widely prescribed monotherapy agent and the principal agent prescribed in combination therapy.

Results of baseline and follow-up attainment of optimal lipid values in our study population are represented in Figure 1 and Table 4. The most recent follow-up value was defined as being at least 6 weeks before prescribing or free of any lipid-modifying medication therapy for 6 weeks. The median baseline LDL-C, HDL-C, TG, and non-HDL-C values for the overall population were 154 mg/dL for LDL-C, 46 mg/dL for HDL-C, 171 mg/dL for TG, and 188 g/dL for non-HDL-C. Non-HDL-C was calculated by subtracting the HDL value from the total cholesterol value.\(^a\)

The distribution of baseline pharmacotherapy for cholesterol disorders is summarized in Table 5. A total of 335 patients (16%) received no drug therapy. Of the 1,784 patients who were prescribed lipid-modifying medication therapy, 1,552 (87%) were prescribed monotherapy and 232 patients (13%) were prescribed combination therapy. The proportion of the different lipid-modifying medications as monotherapy and as combinations was relatively the same across each category. Statins were the most widely prescribed monotherapy agent and the principal agent prescribed in combination therapy.

Results of baseline and follow-up attainment of optimal lipid values in our study population are represented in Figure 1 and Table 4. The most recent follow-up value was defined as being at least 6 weeks after the baseline value. In general, the percentage of patients with lipid goal attainment improved from baseline to follow-up (Figure 1). Improvement in the proportion of patients at LDL-C goal appeared much larger than the proportion of patients who attained goal HDL-C and TG values at follow-up versus baseline. There was a 4-fold increase in the proportion of patients who attained goal values for all 3 serum lipids (LDL-C, HDL-C, and TG), but the absolute proportion was only 32% of patients at follow-up.

Part of the inclusion criteria for the study was that the patients had to be diagnosed as having hyperlipidemia and/or hypercholesterolemia. We analyzed the data to determine the percentage of the study population who might actually have had mixed hyperlipidemia, which we defined as baseline LDL-C greater than the patient’s NCEP ATP III goal based on risk factors, and baseline TG of >150 mg/dL and/or a baseline HDL-C of <40 mg/dL for males or <50 mg/dL for females; 16 patients without gender documentation were excluded from this subpopulation.

According to these criteria, 40% (851/2,119, Table 5) of the population potentially could have been diagnosed with mixed hyperlipidemia rather than hyperlipidemia or hypercholesterolemia at the time of the follow-up lipid values. Among these patients, 21% were meeting the combined lipid goal. In the mixed hyperlipidemia population, 69% of patients were prescribed combination therapy. The proportion of the study population who might actually have had mixed hyperlipidemia, which we defined as baseline LDL-C greater than the patient’s NCEP ATP III goal based on risk factors, and baseline TG of >150 mg/dL and/or a baseline HDL-C of <40 mg/dL for males or <50 mg/dL for females; 16 patients without gender documentation were excluded from this subpopulation.
In our study population, 68% of patients met their LDL-C goal. This level of LDL-C goal attainment is very good compared with similar studies of this nature; however, there is room for improvement. With regard to HDL-C and TG, fewer patients (63% and 59%, respectively) met their goals for these cholesterol parameters than for LDL-C. The proportion of the study population meeting all 3 lipid goals—for LDL-C, HDL-C, and TG combined was only 32%. When looking at the difference between the percentage of patients who were attaining goal for LDL-C, HDL-C, and TG at baseline and those who had obtained lipid goal at their most recent follow-up reading, we found a smaller percentage increase (6%) in the proportion of patients who were meeting their HDL-C goal. There was a modest 18% increase in the number of patients meeting their TG goal. Chi-square analysis of the differences in the number proportion of patients meeting their goal LDL-C, HDL-C, or TG value reveals that there were significant ($P < 0.05$) differences between the baseline and follow-up proportions for all parameters of cholesterol.

When looking at the prescribed medication to treat dyslipidemia in this population, we found the majority of patients (approximately 75%) were prescribed monotherapy with lipid-modifying medication. The statin class of lipid-modifying medications accounted for 89% (1,385/1,552, Table 5) of all monotherapy cholesterol medication prescribed. The different classes of lipid-modifying medications have different effects on cholesterol parameters. The statin class of lipid-modifying medications has the greatest potential to decrease LDL-C, the fibrin acid class has the greatest potential to decrease TG, and the nicotinic acid class has the greatest potential to increase HDL-C. The bile acid sequestrants and the cholesterol absorption inhibitors have a modest effect on lowering LDL-C.

Our analyses also revealed that 40% of the study population potentially had mixed hyperlipidemia. In the mixed hyperlipidemia population, 14% were not prescribed drug therapy; 69% were prescribed monotherapy with lipid-modifying medication, of which 82% was statin monotherapy. Since mixed hyperlipidemia is a cholesterol disorder where multiple lipid parameters are uncontrolled, the choice of a monotherapy statin or any other monotherapy lipid-modifying medication most likely will not be appropriate to get the patient to goal LDL-C, HDL-C, and TG values.

Some physicians may not be considering the entire lipid profile when selecting and monitoring lipid-modifying therapy as evidenced by (1) nearly two thirds of patients were at LDL-C goal; (69%) and HDL-C goal (63%) at follow-up, with the larger magnitude of change in the proportion of patients at LDL-C goal; (2) the prescribing of monotherapy lipid-modifying medications in the majority of the population; and (3) 40% of the study population having mixed hyperlipidemia. Although it is appropriate to adhere to treatment guidelines that uniformly recommend addressing LDL-C as a first step, it is important to realize that this should not be the last step for all patients. Clinical trials strongly support a lower rate of cardiovascular events and reduction in the progression of atherosclerosis or regression of atherosclerosis in trials incorporating HDL-C-raising and TG-lowering strategies in addition to LDL-C lowering. There is strong epidemiological evidence supporting low levels of HDL-C as an independent risk factor for increased CHD morbidity and mortality, and a 1% increase in HDL-C is associated with a 2% to 3% decrease in CHD risk. Conversely, high HDL-C levels have been shown to confer a reduced risk for CHD. It has also been shown that raising HDL-C and lowering levels of TG without lowering LDL-C reduces the rate of coronary events.

**Limitations**

Compliance with cholesterol medication was not an objective of this study, and pharmacy dispensing records were not accessed. Therefore, we could not tie actual patient use of the prescribed lipid-modifying drug therapy with the serum lipid values recorded in the patient chart. Also, data collection may have been inconsistent because we used office personnel who were familiar with the patient charts. This method of data collection pits the tradeoff of familiarity with the methods of medical chart reporting in a given office in an attempt to reduce the opportunity for missing data, with the potential inconsistency in data abstraction that can arise from using a different data abstractor in each medical office. However, this opportunity for inconsistency was minimized through the use of a detailed, uniform training process with each physician practice staff member and the use of a standard data collection tool.

In addition, we relied on medical chart documentation mostly from primary care physician offices. All information of interest may
not have been available at the primary care physician offices, such as the most recent follow-up laboratory values or additional drug therapy that might have been recorded in the office of a cardiologist to whom the patient had been referred by the primary care physician. A more comprehensive data collection method of abstracting data from multiple physician offices seeing each patient was limited by study design because of feasibility and economics. Each patient’s lifestyle, such as diet and exercise routine, was not assessed in this study. Thus, prescribing of lipid-modifying drugs was the only factor assessed in the repeated measure of patient lipid values. Patients with high risk for CHD (e.g., hyperlipidemia and/or hypercholesterolemia) will require lifestyle modifications as well as lipid-modifying medications.7

#### Conclusions

In our study population of patients with a diagnosis of either hyperlipidemia or hypercholesterolemia, 68% met their LDL-C goal at follow-up according to NCEP ATP-III guidelines versus 23% at baseline. A slightly smaller proportion of patients met their HDL-C and TG target goals at follow-up, 63% and 59%, respectively. The proportion of the study population meeting all 3 target goals (LDL-C, HDL-C, and TG) was only 32% but improved from 8% at baseline. Approximately 65% of the study population was prescribed lipid-modifying monotherapy with a statin, 11% was prescribed combination drug therapy, and 16% was not prescribed drug therapy. About 40% of the study population was estimated to have mixed hyperlipidemia, of which 56% was prescribed monotherapy with a statin, 18% was prescribed combination therapy, and 14% was not prescribed drug therapy.

#### What is already known about this subject

Appropriate management of high serum cholesterol can lead to a decreased risk of developing coronary heart disease. Treatment guidelines uniformly recommend addressing LDL-C as a first step. Clinical trials support these guidelines, with a lower rate of cardiovascular events and reduction in the progression of atherosclerosis or regression of atherosclerosis in trials incorporating HDL-C-raising and TG-lowering strategies in addition to LDL-C lowering.

#### What this study adds

This study shows that in real-world high-prescriber practices, there seems to be less than optimal focus on treating the entire lipid profile of LDL-C, HDL-C, and TG.

#### DISCLOSURES

Funding for this study was provided through a grant from Kos Pharmaceuticals to Total Therapeutic Management, Inc., employer of authors Thomas A. Stacy and Allison Egger. Stacy served as principal author of the study. Study concept and design were primarily contributed by Stacy; with input from Egger. Data collection was the work of both authors; data interpretation was primarily the work of Egger, with input from Stacy. Writing of the manuscript and its revision were primarily the work of Stacy, with input from Egger.

#### REFERENCES

Adherence, Compliance, and Persistence

• Patient adherence with amlodipine, lisinopril, or valsartan therapy in a usual-care setting. 2003;9(5):424-29.
• Measuring adherence and persistence in drug therapy. 2002;8(3):204-46.
• Patient adherence with HMG reductase inhibitor therapy among users of two types of prescription services. 2002;8(3):186-91.
• Adherence, compliance, and persistence in drug therapy. 2002;8(3):177-78.
• A team approach to address antiretroviral therapy adherence barriers in a managed care organization. 2001;7(3):214-18.
• Evaluating medication adherence: which measure is right for your program? 2000;6(6):499-504.

Behavioral Health


Biotechnology


Capitation and Risk-Financing Methods

• Contractual arrangements between HMOs and medical groups to manage drug costs (editorial). 2003;9(6):572.
• Medical errors, adverse medical events, and PDRM. 2002;8(5):400.
• Mississippi Medicaid waiver breaks new ground for pharmacists. 1996;2(6):564, 566.

Adverse Drug Events

• Indicators of preventable drug-related morbidity in older adults. 2. Use within a managed care organization. 2003;9(2):134-41.
• Medical errors, adverse medical events, and PDRM. 2002;8(5):400.
• Evaluation of resources used to treat adverse events of selective serotonin reuptake inhibitor use. 2001;7(5):402-06.
• Adverse drug events: a plea for reporting and new rules to ease the burden. 1998;4(4):364.

Clinical Pharmacy—Patient Consultation

• Pharmacists should assume a larger role in overcoming the racial/ethnic barriers to breast cancer screening (letter). 2006;12(5):406-07.
Clinical Pharmacy Interventions—
Quality, Service, and Cost Outcomes

- Experience with a clinical decision support system in community pharmacies to recommend narrow-spectrum antimicrobials, nonantimicrobial prescriptions, and OTC products to decrease broad-spectrum antimicrobial use. 2006;12(5):390-97.
- Assessment of patient satisfaction with telephone and mail interventions provided by a clinical pharmacy cardiac risk reduction service. 2005;11(5):403-09.
- Clinical pharmacist interventions to bridge the quality chasm and methods necessary to hold quality improvement gains (editorial). 2004;10(2):167-68.
- Assessment of clinical pharmacist management of lipid-lowering therapy in a primary care setting. 2003;9(3):269-73.
- Determining the value of pharmacy services—the search for rigorous research designs. 2002;8(2):152-53.

Clinical Pharmacy Quality Improvement—
Patient Safety and Prevention of ADEs

- Preventing medication errors and adverse drug events. 2003;9(1):92-93.

Clinical Practice Guidelines (CPGs) and Quality Improvement

- Liver and thyroid monitoring in ambulatory patients prescribed amiodarone in 10 HMOs. 2006;12(8):656-64.
- Evidence-based medicine: beware of results from randomized controlled trials and research with administrative claims data (editorial). 2005;11(2):172.
- Cross the quality chasm—incremental change through clinical practice guidelines (CPGs) (editorial ). 2002;8(5):400-01.
Clinical Quality Improvement

- Framework for pharmacy services quality improvement—a bridge to cross the quality chasm. 2004;10(1):60-78.
- Managing drug therapy decisions: pay me now or pay me later. 1998;4(3):242, 245.

Collaboration—Pharmacists and Others

- Pharmacy practice in the long-term care environment. 1997;3(2):189-94.

Collaboration—Pharmacy Education

- Oregon State University partners with Medicaid and a managed care organization. 2001;7(3):185-86.
- The University of Colorado School of Pharmacy and the University of Colorado Health Plan forge a PBM partnership. 1998;4(5):478, 480.

Collaborative Practice—Pharmacists as Prescribers


Database Analyses of Drug Utilization (see also Research Methods)

- Categorizing patients from medical claims data—the influence of GIGO (letter). 2004;10(6):559-60.
- Claims data and drawing appropriate conclusions. 2002;8(2):152.

Decision Support Systems (DSS)


Direct-to-Consumer Advertising (DTCA) (see also Drug Promotion and Advertising)

- United States, the last venue for direct-to-consumer advertising, props up the erectile dysfunction market (editorial). 2005;11(2):176-78.
- Direct-to-patient advertising (DTPA) and direct-to-consumer advertising (DTCA) of prescription drugs. 2002;8(6):521.

Disease Management—Airway Disease or Allergic Rhinitis

- Health care utilization determined from administrative claims analysis for patients who received inhaled corticosteroids with either montelukast or salmeterol (letter). 2006;12(6):486-87.
More evolution of the evidence in asthma disease management—SMART versus GOAL clinical trials debate the cost-benefit of LABA while the value of leukotriene modifiers, particularly montelukast, is uncertain (editorial). 2006;12(4):343-46.


• Administrative claims analysis of asthma-related health care utilization for patients who received inhaled corticosteroids with either montelukast or salmeterol as combination therapy. 2006;12(4):310-21.


• Asthma disease management—evidence-based medicine must be dynamic. 2006;12(1):80-82.

• Analysis of the effectiveness and cost benefit of leukotriene modifiers in adults with asthma in the Ohio Medicaid population. 2006;12(1):33-42.

• Selectivity and specificity are the keys to cost-effective use of omalizumab for allergic asthma (editorial). 2005;11(9):774-76.

• Evaluation of omalizumab from a health plan perspective. 2005;11(9):735-45.


• New concepts to improve health outcomes for patients with chronic obstructive pulmonary disease (supplement). 2005;11(6, S-a):S1-S22.

• Contemporary issues in the care of patients with chronic obstructive pulmonary disease (supplement). 2005;11(5, S-a):S1-S16.


• Alternate managed care approaches to disease management of allergic rhinitis (editorial). 2004;10(3):257.


• Pediatric asthma: improving management to reduce cost of care. 2004;10(2):130-41.


• Enhancing value-based decision-making: allergic rhinitis (supplement). 2004;10(1, S-a):S1-S17.


• Optimizing clinical and economic outcomes in asthma management: individualizing drug therapy to address dual components of asthma (supplement). 2002;8(5):S1-S25.


• Evaluating asthma medication use before and after an acute asthma-related event. 2001;7(4):303-08.


• Review of eight pharmacoeconomic studies of the value of biologic (adalimumab, etanercept, and infliximab) in the management of rheumatoid arthritis. 2006;12(7):555-69.
<table>
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<th>Article Index</th>
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<tr>
<td>• COX-2 inhibitors: little or no GI protection, increased risk of cardiovascular events, high cost, and other class-less effects (editorial). 2005;11(7):590-93.</td>
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<tr>
<td>• Gastrointestinal bleeding rates among managed care patients newly started on COX-2 inhibitors or nonselective NSAIDs. 2005;11(7):550-58.</td>
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<tr>
<td>• Relationship of clinical factors to the use of COX-2 selective NSAIDs within an arthritis population in a large HMO. 2002;8(4):252-58.</td>
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<tr>
<td>• Economic considerations in the management of arthritis. 1999;5(6):476-78, 481-82, 484.</td>
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**Disease Management—Atopic Dermatitis**


**Disease Management—Attention-Deficit/ Hyperactivity Disorder (ADHD)**


**Disease Management—Benign Prostatic Hyperplasia**


**Disease Management—Cancer**


**Disease Management—Depression or Bipolar Disorder**

- Comparison of mental health resources used by patients with bipolar disorder treated with risperidone, olanzapine, or quetiapine. 2005;11(3):220-30.
- Evidence-based medicine: are SSRIs more effective than placebo and what length of therapy is enough? (editorial). 2005;11(2):172-76.
- Relationship of total health care charges to selective serotonin reuptake inhibitor utilization patterns including the length of antidepressant therapy—results from a managed care administrative claims database. 2005;11(2):145-50.

**Disease Management—Diabetes**

• Physician conformity and patient adherence to ACE inhibitors and ARBs in patients with diabetes, with and without renal disease and hypertension, in a Medicaid managed care organization. 2006;12(8):649-55.
• Total and component health care costs in a non-Medicare HMO population of patients with and without type 2 diabetes and with and without macrovascular disease. 2006;12(7):548-54.
• What are incretins, and how will they influence the management of type 2 diabetes? (supplement). 2006;12(7, S-a):S1-S16.
• Relationship of oral antihyperglycemic (sulfonylurea or metformin) medication adherence and hemoglobin A1c goal attainment for HMO patients enrolled in a diabetes disease management program. 2006;12(6):466-71.
• Blood pressure goal attainment according to JNC 7 guidelines and utilization of antihypertensive drug therapy in MCO patients with type 1 or type 2 diabetes. 2006;12(4):303-09.
• Economic impact of antidiabetic medications and glycemic control on managed care organizations: a review of the literature. 2006;12(2):130-42.
• Utilization and costs for compliant patients initiating therapy with pioglitazone or rosiglitazone versus insulin in a Medicaid fee-for-service population. 2006;12(2):121-29.
• Relationship of glycemic control to total diabetes-related costs for managed care health plan members with type 2 diabetes. 2005;11(7):559-64.

Disease Management—Dyslipidemia

• Results of retrospective chart review to determine improvement in lipid goal attainment in patients treated by high-volume prescribers of lipid-modifying drugs. 2006;12(9):745-51.
• Lipid levels and use of lipid-lowering drugs for patients in pharmacist-managed lipid clinics versus usual care in 2 VA medical centers. 2005;11(9):763-71.
• Clinical and economic outcomes of conversion of simvastatin to lovastatin in a group-model health maintenance organization. 2005;11(8):681-86.
• Fish oil for heart disease—happy to be in second place (editorial). 2005;11(7):584-85.
• Similar medication compliance and control of dyslipidemia with simvastatin or atorvastatin in a staff-model HMO medical clinic. 2005;11(6):499-504.
• Quantifying the effect of applying the NCEP ATP III criteria in a managed care population treated with statin therapy. 2004;10(3):244-50.
• Effective cholesterol management with fewer dollars. 2002;8(6):519.
• High blood cholesterol and ATPIII: guidelines for health benefit and health care providers. 2001;7(6):482-89.

Disease Management—Heartburn
• Employers need to have a wider horizon than drug costs alone when considering the implementation of health care intervention programs (letter and author response). 2006;12(7):581-83.
• PPIs are therapeutically interchangeable and ideal for a managed care intervention such as therapeutic MAC (editorial). 2006;12(7):578-80.
• Peptic acid disorders: developing a disease management program. 1996;2(5):569-75.

Disease Management—Irritable Bowel Syndrome

Disease Management—Kidney Disease
• Assessment of time and practice resources required to provide weekly or monthly erythropoiesis-stimulating protein therapy to chronic kidney disease patients in the physician office setting. 2006;12(9):714-25.

Disease Management—Migraine Syndrome
• Assessment of clinical, service, and cost outcomes of a conversion program of sumatriptan to rizatriptan ODT in primary care patients with migraine headaches. 2006;12(3):246-53.
Disease Management—Obesity

- Which is more elusive, the pot of gold at the end of a rainbow or determining the most cost-effective triptan? (editorial). 2005;11(6):513-15.
- Triptans for migraine therapy: a comparison based on number needed to treat and doses needed to treat. 2005;11(5):394-402.
- Meta-analysis of oral triptan therapy for migraine: number needed to treat and relative cost to achieve relief within 2 hours. 2003;9(1):45-52.

Disease Management—Multiple Sclerosis


Disease Management—Psoriasis

Disease Management—Seizure Disorders and Epilepsy

• Step therapy is not appropriate for antiepileptic drugs (letter). 2006;12(3):269-70.

Disease Management—Thrombosis, DVT, and VTE

• Effect of a clinical pharmacy education program on improvement in the quantity and quality of venous thromboembolism prophylaxis for medically ill patients. 2005;11(9):755-62.
• In search of safe and effective oral anticoagulation (editorial). 2005;11(8):704-08.
• Longitudinal evaluation of health plan cost per venous thromboembolism or bleed event in patients with a prior venous thromboembolism event during hospitalization. 2005;11(8):663-73.
• Quality improvement in the continuum of care: impact of atherosclerosis in managed care pharmacy (supplement). 2004;10(6, S-a):S1-S16.

Disease Pathology


Dose Optimization

• Initial results of the use of prescription order change forms to achieve dose form optimization (consolidation and tablet splitting) of SSRI antidepressants in a state Medicaid program. 2006;12(6):449-56.
• Dose consolidation can be an efficient intervention. And author response (letters). 2004;10(6):564-66.
• Randomized controlled trial of a dose consolidation program. 2004;10(5):396-403.
• Dose-optimization intervention yields significant drug cost savings. 2002;8(2):146-51.
• Dose optimization: an opportunity for pharmacy administrative services. 2002;8(2):81.

Drug Benefit Management—Benchmarks and Measures

• Principles and practical applications of benchmarking (supplement). 2005;11(1, S-a):S1-S23.
• Other DACON observations—community pharmacists do not intentionally transmit incorrect claim information—but caution is warranted in days supply calculations (letter). 2004;10(2):174-75.
• Need for greater scrutiny of days supply values in DACON calculations (letter). 2004;10(2):172-73.
• Searching for drug benefit benchmarks—cost per day of therapy. 2002;8(1):54-55.

Drug Benefit Management—Benefit Design

• Relationship of the use and costs of physician office visits and prescription drugs to travel distance and increases in member cost share. 2006;12(8):665-76.
• Cost reduction strategies used by elderly patients with chronic obstructive pulmonary disease to cope with a generic-only pharmacy benefit. 2006;12(5):377-82.
• The estimated impact of drug importation, mandatory mail service, and Medicaid fee reduction on community pharmacies in Michigan. 2006;12(2):157-63.
• A 30-month evaluation of the effects on cost and utilization of proton pump inhibitors from adding omeprazole OTC to drug benefit coverage in a state employee health plan. 2006;12(1):25-32.
• The role of pharmaceuticals in reducing cardiometabolic risk: rethinking pharmacy benefit design to reduce the burden on the health care system (supplement). 2006;12(1):S1-S16.
• Effects on the cost and utilization of proton pump inhibitors from adding over-the-counter omeprazole to drug benefit coverage in a state employee health plan. 2004;10(5):449-55.
• Does member cost-sharing pose a threat to desirable patient outcomes? 2004;10(3):256.
• 3-tier drug benefit designs based on sound drug formulary principles will maximize favorable outcomes (editorial). 2004;10(1):83-84.
• Benefit maximums versus drug benefit needs for Medicare beneficiaries. 2002;8(5):402-03.
Prescription use behavior among Medicare beneficiaries with capped prescription benefits. 2002;8(5):360-64.

Drug Benefit Management—Efficiency and Patient Safety
Weight uniformity of split tablets required by a Veterans Affairs policy. 2003;9(3):401-07.
Tablet splitting to improve the value-for-money equation in cholesterol management. 2002;8(6):519.

Drug Benefit Management—Employee Benefits and Coverage (see also Drug Benefit Management—Benefit Design)
Anticipating the future: how the emergence of innovative biologic agents impacts benefit design, utilization, and provider relations (supplement). 2004;10(3, S-a):S1-S20.
New generic and OTC drugs provide opportunities for drug benefit managers. 2002;8(6):520.
Successful disease management programs for health and welfare fund union groups. 1998;4(3):269-70, 272.

Drug Benefit Management—Patient Satisfaction, Benefit Knowledge, and Consumer Behavior
Drugs, PPOs, tiered cost-share for beneficiaries, and consumer preferences. 2002;8(3):177.
Patient satisfaction with and knowledge of their prescription drug coverage. 2001;7(1):34-42.
Article Index


Drug Benefit Management—Pharmacy Providers


Drug Benefit Management—Quantity Limits, Step Therapy, and Prior Authorization (PA) and Rebates

- Utilization and cost of sildenafil in a large managed care organization with a quantity limit on sildenafil. 2005;11(8):674-80.
- Evaluation of a monthly coverage maximum (drug specific quantity limit) on the 5-HT1 agonists (triptans) and dihydroergotamine nasal spray. 2003;9(4):335-45.
- Analysis of a prescription drug prior authorization program in a Medicaid health maintenance organization. 2003;9(1):36-44.
- Medical and pharmacy cost and utilization outcomes of a quantity limit on 5-HT1 agonists (triptans) by a managed care organization. 2001;7(6):468-75.

Drug Benefit Management—Pharmacy Providers


Drug Benefit Management Methods—Benefit Design

- Prescription use behavior among Medicare beneficiaries with capped prescription benefits. 2002;8(5):360-64.

Drug Promotion and Advertising (see also Direct-to-Consumer Advertising [DTCA])

- Information requirements of health systems as drug purchasers: does the FDA have a role in setting evidentiary standards? 1996;2(6):593-98.

Drug Spending, Utilization, and Cost Trends

- Too much or too little? The role of pharmaceuticals in the health care system. 1999;5(4):296-97, 301-02.
Local area market dynamics. 1998;4(2):115-17, 120.

Drug Therapy—Natural Products

Drug Therapy, Therapeutic Selection, and P&T Decision Making
- Pharmacist intervention in safe and effective conversion of brand to generic drugs (letter). 2005;11(9):777.
- Comparison of costs and utilization between users of insulin lispro versus users of regular insulin in a managed care setting. 2005;11(5):376-82.
- Cost and utilization comparisons among propensity score-matched insulin lispro and regular insulin users. 2003;9(3):263-68.
- Improvements in glycemic control in type 2 diabetes patients switched form sulfonylurea coadministered with metformin to glyburide-metformin tablets. 2003;9(3):256-62.

Drug Utilization Review (DUR) or Drug Utilization Management—Appropriate Drug Use
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- Comparison of rates of potentially inappropriate medication use according to the Zhan criteria for VA versus private sector Medicare HMOs. 2006;12(5):362-70.
- Gabapentin may be appropriate for off-label uses (editorial). 2003;9(6):569-70.
- Examination of the evidence for off-label use of gabapentin. 2003;9(6):559-68.

**Ethics**


**Formulary Management—Methods and Effects—Pharmacoeconomics**

- P&T committees—black boxes versus AMCP Format, and what is the true cost and value of pimecrolimus (editorial). 2005;11(1):93-94.


Meta-analysis of oral triptan therapy for migraine: number needed to treat and relative cost to achieve relief within 2 hours. 2003;9(1):45-52.


Exploring the methodological challenges of investigating comparison groups with different underlying characteristics: a case study. 2002;8(5):353-59.


The role of pharmacoeconomic information in the formulary decision-making process. 2000;6(2):108, 113-14, 117-18, 121.


DOD’s Pharmacoeconomic Center: translating research into good patient care practices. 1997;3(6):662-64,666.


Development of a complementary and alternative medicine (CAM) pharmacy and therapeutics (P&T) subcommittee and CAM guide for providers. 2005;11(3):252-58.


International markets offer new opportunities for MCOs and PBMs. 1997;3(4):403-04,409-10.


Alternative medicine in managed care pharmacy. 1997;3(1):77-80,83-86.

Indian Health Service: paving the way for pharmaceutical care. 1997;3(1):36,41-43.


Information technology to cross the quality chasm. 2002;8(5):401-02.

Quality improvement opportunities in health care—making it easy to do it right. 2002;8(5):394-99.

• Medical and medication errors: a partial summary of reports by the Institute of Medicine and the quality interagency coordination task force. 2001;7(1):62-68.
• How to evaluate disease state management programs. 1997;3(3):270, 273-74, 277-78.
• Managed care and the quest for quality measures. 1997;3(3):255, 258-89.
• Successful CQI-based programs in a group-model managed care setting. 1995;1(2):134, 137.

Health Care Spending and Health Economics
• Is there no prescription to decrease health care outlays in the face of an aging population? 2000;6(3):51-54.
• Health economics II: some unique aspects of health economics. 2000;6(2):173-78.

Health Insurance and Health Care Finance
• Direct contracting: the next purchaser strategy. 1999;5(2):11-12, 14, 16.
• Blue Cross and Blue Shield: making pharmaceutical care a key component of managed care. 1996;2(1):33-34, 36, 38.
• Professional opportunities in managed care pharmacy. 1995;1(2):80, 82, 86-87.

Lifestyle Drugs

Managed Care Pharmacy Practice
• Quality articles require peer reviewers—as well as authors (letter). 2005;11(2):186.
• John Ogden talks about managed care in the Veterans Administration. 2002;8(2):91-93.
• Managed care and the pharmacy profession revisited. 1999;5(2):78.
• The importance of communication skills for the managed care pharmacist. 1998;4(2):102.
• The changing face of managed care pharmacy and the role of PBMs. 1997;3(5):494, 497-98.
• Blue Cross and Blue Shield: making pharmaceutical care a key component of managed care. 1996;2(1):33-34, 36, 38.
• Professional opportunities in managed care pharmacy. 1995;1(2):80, 82, 86-87.

Managed Health Care

• Medicare PPOs and managed care. 2003;9(1):91.
• Examining the managed health care continuum. 1997; 3(5):511-12, 515-16, 518.

Manpower and Job Satisfaction

• A closer look at pharmacy technicians. 2003;9(1):84.
• How many pharmacists are in our future? The Bureau of Health Professions projects supply to 2020. 2000;6(6):474-82.
• Burnout in a sample of HMO pharmacists using the Maslach Burnout Inventory. 1998;4(3):495-503.

Medicaid


Medicare and Medication Therapy Management (see also Drug Benefit Management Methods—Benefit Design)

• Timeline and potential impact of CMS's drug Competitive Acquisition Program (CAP). 2006;12(3):263-64.
• Medication Therapy Management Services for long-term care patients: no road maps for those trying to find their way (editorial). 2005;11(7):586-87.

Pain Management

• Beyond narcotics for effective pain management. 2003; 9(2): 175-76.
• It’s a pain. 1999;5(6):558.

Pharmaceutical Industry and Marketing

• Product-line extensions and pricing strategies of brand-name drugs facing patent expiration. 2005;11(9):746-54.
• India’s pharmaceutical industry: a growing influential force in the world pharmaceutical market. 2002;8(3):211-15.

Pharmacogenomics

• Drug therapy customized to individual patients. 2002;8(4):296-97.
• Health care professionals’ perceptions of the role of pharmacogenomic data. 2002;8(4):278-84.

Pharmacy Education

• Managed care and the University of Texas College of Pharmacy. 2001;7(6):490.
University of Michigan College of Pharmacy and managed care partner to enhance drug therapy. 2001;7(5):345-46.

An inside look at the benefits of a student pharmacy and therapeutics (P&T) committee competition from the University of Illinois at Chicago. 2001;7(4):259-60.

Managed care concepts prominently featured in innovative management programs at Duquesne University. 2001;7(2):94,96.


The University of Maryland's Center on Drugs and Public Policy. 2000;6(2):184-85.


Managed care pharmacy practice at the Texas Tech University Health Sciences Center School of Pharmacy. 1999;5(6):556-57.

Description of a formal affiliation between a school of pharmacy and a managed care organization. 1999;5(5):433-37.


Improving efficiency and effectiveness in managed care: ongoing efforts at the University of New Mexico College of Pharmacy. 1999;5(2):111.


First managed care pharmacy course at the University of Illinois at Chicago. 1998;4(1):80-81.


Pharmacy internship offers real-world exposure to managed care pharmacy practice. 1996;2(6):605-06.

Managed care pharmacy at the St. Louis College of Pharmacy. 1996;2(4):439, 442.


Managed care pharmacy education at the University of Washington School of Pharmacy. 1996;2(3):319-20.

Managed care pharmacy education at MCP. 1996;2(1):53.

Physician Education-Intervention—Academic Detailing


Selection bias in physician education-intervention programs. 2002;8(2):82.


UIC students mobilize first student chapter of AMCP. 1995;1(3):185-86.

Population Health—Interventions and Prevention of ADEs

Suboptimal pneumococcal pneumonia vaccination rates among patients at risk in a managed care organization in Israel. 2006;12(3):152-56.


Prior Authorization (PA) (see Drug Benefit Management—Quantity Limits, Step Therapy, and Prior Authorization [PA])

Privacy of Health Information


The Health Insurance Portability and Accountability Act of 1996 (HIPAA) and the pharmacy benefit: implications for health plans, PBMs, and providers. 2003;9(1):66-71.


Quality Assurance

Research Methods (see also Survey Methods)
• Conjoint analysis in pharmaceutical research. 2002;8(3):206-08.
• Researching managed care pharmacy using Internet searches. 2001;7(3):201-04, 213.
• Method is everything: evaluating results by study design. 1997;3(1):66-68, 71-72, 75-76.
• Epidemiological techniques. 1997;3(1):30-32, 35.
• Interface between pharmacoepidemiology and pharmacoeconomics in managed care pharmacy. 1996;2(3):282-89.
• Outcomes research, pharmacoeconomics, and the pharmaceutical industry. 1996;2(1):48-52.

Safety—Health Care Worker

Safety—Patient Care (see Drug Utilization Review [DUR])

Specialty Pharmacy
• Specialty pharmacy cost management strategies of private health care payers. 2006;12(9):736-44.
• The emergence of specialty pharmacy. 2000;6(4):280-84.

Survey Methods (see also Research Methods)
• Constructing mail survey questionnaires to maximize the rates of return and assure the validity and reliability of responses. 2002;8(3):225-31.

Technology—Automation

Technology—Education and Information
• Use of technology throughout the curriculum. 2002;8(2):86.
• Automation aids prescription processing—but professional judgment remains indispensable. 1995;1(2):90, 93-95.

Technology—Electronic Prescribing
• Standardization is necessary in the methods to assess the value of electronic prescribing systems (letter). 2005;11(7):594-95.
• Extent of electronic prescribing implementation as perceived by MCO pharmacy managers. 2002;8(1):41-47.

Therapeutic Interchange—Therapeutic Selection

• Utilization of pharmacy claims data to evaluate therapeutic interchange programs. 1999; 5(4):331-34.

Value of Pharmacotherapy

• RxHealthValue offers three recommendations and cost research. 2001; 7(1):17-20.

Women’s Health