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October is National Pharmacy Month—designated to increase patient awareness of the proper procedures for taking prescription drugs.

Many such promotional efforts have taken place in the past. For instance, in the early 1930s, the House of Delegates at the American Pharmaceutical Association (APhA) urged the adoption of a United States commemorative postage stamp honoring the profession of American pharmacy. Ideally, the stamp’s introduction would have coincided with the 1934 dedication of the organization’s newly completed national headquarters in Washington, D.C. But 38 years would pass before the 8-cent Pharmacy stamp was finally issued on November 10, 1972.

According to the March/April 2002 issue of the Journal of the American Pharmaceutical Association, “The issuance of the 1972 Pharmacy stamp was made possible by the unified and persistent effort of individuals from all sectors of the profession, including academia, associations, community, industry, and students. From 1939 to 1940, Parke-Davis officials initiated a national grassroots campaign to garner support for a commemorative pharmacy stamp but the time was not ripe. However, a resurgence of community grassroots activism in the 1960s led by influential pharmacists, such as George Griffenhagen and Irving Rubin, led to the approval of the commemorative Pharmacy stamp by the U.S. Postal Service. Approximately 165,895,000 stamps were printed utilizing the intaglio method on offset and Giori presses. Designed by artist Ken Davies, the stamp depicts a still-life scene with the Bowl of Hygeia (symbol of APhA), a Wedgwood mortar and pestle with an ‘Rx’ inscription (symbol of the National Association of Retail Pharmacists—NARD), and two 19th-century glass tincture bottles.” Davies told Griffenhagen that he made the names on the bottles illegible “so that there could be no specific mention of any one drug or potion.”

Born in 1925 in New Bedford, Massachusetts, Davies described his personal history, posted on AskART’s Web site: “In the early years, I did three pieces of work that were major milestones for me and which have determined the course of my painting career. The first of the three was a drawing I did in the fourth grade. My teacher, Miss Sweeney, had decided to turn an art assignment into a class competition. When she announced her decision, I had won first prize! This was pretty heady stuff, and it became obvious to me that my lifework would now be in art.” He continued by saying that his second important work of art was created when he was a freshman at the Massachusetts School of Art in Boston. It was the first oil painting he ever did, and he declared the medium “love at first sight” after struggling with watercolor for several years. Davies’s third significant piece was a still-life painting, done while he was a junior at the Yale School of Art. This work sparked his interest in trompe l’oeil (French for “trick the eye”). In fact, he wrote his bachelor of fine arts thesis on the history of trompe l’oeil painting. Davies graduated from Yale in 1950 and immediately embarked on his teaching career. He spent three years at the Whitney School of Art in New Haven, Connecticut, and then moved on to the Paier School of Art in Hamden, Connecticut, where he taught for four years and served as dean from 1958 to 1981.

Davies did some commercial art work early in his career such as story illustrations for The Saturday Evening Post and Collier’s magazines. His most notable project was the turkey logo he created for Austin Nichols’s Wild Turkey bourbon. Davies’s paintings have been widely exhibited throughout the country, and his work is housed in numerous public, corporate, and private collections. They include the White House and Smithsonian American Art Museum, Washington, D.C.; Detroit Institute of Art; Springfield Museum of Fine Arts, Springfield, Massachusetts; Berkshire Museum, Pittsfield, Massachusetts; General Mills, Minneapolis, Minnesota; and Union Carbide Corporation, Houston, Texas.

Ronald Cavalier, Jr., of Cavalier Galleries in Greenwich, Connecticut, has called Davies “The Master of the American Still Life.” And the artist’s success as a Realist painter inspired a reviewer in Art Digest to write: “Ken Davies’s trompe l’oeil paintings exhibit a visual observation so acute and a technical handling so precise that the spectator is not willing to give up the illusion that he can actually grasp a pencil or tear a piece from a torn envelope until he is within a foot of the canvas.”

Davies finds most of the props for his still lifes at antique shops. He said, “I never know what I’ll find—it’s always a thrill to discover objects that inspire a new painting.”

Among Davies’s many honors are awards from the Springfield and Berkshire museums, the Connecticut Academy of Fine Arts, the Silvermine Guild of Artists, and a grant from the Louis Comfort Tiffany Foundation. His work has been featured in Art & Antiques, American Artist, and American Art Review magazines, and he is the author of two books: Painting Sharp Focus Still Lifes, and Ken Davies: Artist at Work.

Sheila Macho
Cover Editor

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Direct Medical Costs of Venous Thromboembolism and Subsequent Hospital Readmission Rates: An Administrative Claims Analysis From 30 Managed Care Organizations

Alex C. Spyropoulos, MD, FACP, FCCP, and Jay Lin, PhD, MBA

ABSTRACT

BACKGROUND: Venous thromboembolism (VTE) is a common medical condition manifested as deep vein thrombosis (DVT) or pulmonary embolism (PE). Few data exist on the total economic burden of DVT and PE.

OBJECTIVE: To (1) quantify the economic burden of DVT and PE in direct medical costs and utilization and (2) determine the rates of hospital readmission for DVT and PE.

METHODS: Hospital claims containing DVT or PE as a primary or secondary discharge diagnosis during the period February 1998 through June 2004 were identified by retrospective analysis using the Integrated Health Care Information Services (IHCIS) National Managed Care Database. For the cost analysis, we included patients that had been enrolled in a health care plan for a minimum of 30 days prior to and 365 days following the DVT or PE hospitalization. For the readmission analysis, patients were required to have a minimum length of stay of 3 days and a reenrollment of 365 days. We quantified the cost burden to the health plan by examining annual DVT- and PE-related payments made by the health plan to providers for inpatient and outpatient care.

RESULTS: Of 5 million plus discharges in the database with dates of service between February 1, 1998, and June 30, 2004, 32,193 (0.64%) had DVT or PE as a primary discharge diagnosis, and 26,159 (0.52%) had DVT or PE as a secondary discharge diagnosis. After application of the inclusion and exclusion criteria, there were 5,348 patients with a primary discharge diagnosis of DVT and 4,593 patients with a secondary discharge diagnosis of DVT. For PE, 2,984 patients had a primary discharge diagnosis, and 1,119 had a secondary discharge diagnosis. The hospital readmission rates within 1 year for the combined diagnoses (DVT or PE) were 5.3% for primary and 14.3% for secondary diagnoses; 44.3% of the PE readmissions occurred within the first 30 days. Within 90 days, 50.7% of DVT readmissions and 58.6% of PE readmissions occurred. Regarding cost for a primary diagnosis, the average total annual provider payments made by a health plan were $10,804 for DVT and $16,644 for PE. For secondary diagnoses, the average total annual costs were $7,594 for DVT and $13,018 for PE. The mean hospital cost per readmission for a recurrent DVT ($11,862) was higher than the mean cost for the initial hospitalization ($9,805, P = 0.006), but the mean cost per PE readmission ($14,722) was similar to the mean cost for the initial hospitalization ($14,146, P = 0.38).

CONCLUSIONS: The economic burden of DVT and PE in direct medical cost is large, due not only to the initial hospitalization event, but also to the high rate of hospital readmission (5%-14%), over half of which occurs within 90 days.

KEYWORDS: Cost, Deep vein thrombosis, Pulmonary embolism, Venous thromboembolism, Recurrence, Managed care, Economic burden

J Manag Care Pharm. 2007;13(6):475-86

What is already known about this subject

- VTE is a common medical condition of particular importance in the hospital setting. In patients with major surgery, the diagnosis and treatment of an initial VTE event poses a significant economic burden to health care in the United States.
- The diagnosis and treatment of the initial VTE event incurs costs, but the VTE recurrences and long-term complications of VTE create additional costs. It was found previously that 1 in 4 patients who experienced a VTE event during the incident hospital stay had additional VTE-related events requiring hospitalization in the 21 months of follow-up. These events incurred an average health plan cost of $14,957 per event, or $2,101 per patient per year.

What this study adds

- The total annual health care cost for a VTE ranged from $7,594 to $16,644, depending on the type of event and whether it was a primary or secondary diagnosis. The hospital readmission rates of DVT or PE within 12 months were 5.3% for primary and 14.3% for secondary diagnoses.
- The recurrent DVT event was associated with 21% greater cost compared with the initial DVT event, but there was no difference in cost for the recurrent PE event compared with the initial PE event.
- The use of health plan total medical costs, including outpatient medical and pharmacy in this study, resulted in higher total costs compared with previous studies that used hospital inpatient costs.

V enous thromboembolism (VTE) is a common medical condition comprising deep vein thrombosis (DVT) and pulmonary embolism (PE). VTE is of particular importance in the hospital setting since more than half the cases of VTE are accounted for by institutionalization, with 24% of the cases attributable to hospitalization for surgery. In the absence of prophylaxis, the incidence of objectively confirmed, hospital-acquired DVT ranges from 10% to 40% in the medical and general surgical population to as high as 40% to 60% in patients who have undergone orthopedic surgery. Furthermore,
in patients who have undergone major orthopedic surgery, the mortality rate due to VTE can be as high as 5%, underscoring the very high-risk nature of this population. Recent estimates for the incidence of VTE in the United States suggest that VTE occurs, for the first time, in 100 to 120 of every 100,000 (~0.1%) of the population yearly.

Few data exist on the overall economic burden of VTE; however, Botteman et al. constructed a model to assess cost-effectiveness of DVT prophylaxis in total hip replacement (THR) in the United States. They estimated the cost of diagnosis and treatment of DVT at $4,159 and PE at $5,567. Other analyses have provided data on the economic burden of VTE via cost-effectiveness studies of prophylaxis versus no prophylaxis.

A study of administrative claim records for January 1, 1997, through March 31, 2004, found that the median annualized medical costs of patients during and after the DVT or PE event were $17,512 and $18,901, respectively.

It is also important to note that the economic burden of VTE is not confined to the diagnosis and treatment of the initial event. Previous studies have demonstrated that a history of VTE is a strong independent risk factor for recurrent VTE in medical patients. Furthermore, 7% to 14% of patients with a VTE will have a recurrent event within 1 year, a figure that rises to approximately 30% at 10 years. It has been established that, in high-risk surgical patients, the majority of recurrent VTE occurs shortly after the initial event, most frequently in the first 3 months. These types of readmissions, especially within 30 days of the original hospital discharge, represent a major concern of quality patient care at hospitals. Moreover, the type of recurrent VTE episode appears to be strongly correlated to the initial VTE. For example, DVT accounted for 86% of recurrent VTE after an initial DVT, and PE accounted for 66% of recurrent VTE after an initial PE. In addition to recurrent VTE, other long-term complications include postthrombotic syndrome and pulmonary hypertension.

The extended cost of long-term complications of VTE has been investigated in a small number of studies. In patients who had undergone THR, the average lifetime costs associated with long-term complications of VTE was $3,069 per patient. Similarly, in the study by Botteman et al., the annual cost of long-term events in patients with VTE after THR was $3,798 for DVT and $6,404 for PE. In an analysis of administrative claims from 2 large U.S. health care plans, Bullano et al. found during a 21-month follow-up of patients who experienced a VTE event that 13.4% of patients experienced an average of 1.26 recurrent VTE events that required hospitalization, with an average cost of $5,736 per event.

Although data exist to show that VTE and its sequelae pose a considerable medical problem, little data exist on the absolute cost burden of VTE. The present study therefore used actual health care plan reimbursement costs compiled in a large managed care database, containing records from across the United States, to investigate the cost burden of not only initial but also hospital readmission for DVT and PE in the general population. The costs associated with a primary diagnosis of VTE are relatively clear as being all costs included during that hospitalization. Patients with VTE as a secondary diagnosis (and therefore with comorbidities) represent an interesting group to compare costs against patients with VTE as a primary diagnosis, since not all hospital costs of these patients are associated with the VTE event. Therefore, this study also investigated the costs associated with DVT and PE in patients with VTE as a secondary diagnosis.

### Methods

#### Data Source

This study was a retrospective observational cohort analysis utilizing data from the Integrated Health Care Information Services (IHCIS) National Managed Care Database, which contains claim information from approximately 30 managed care organizations and comprises patient records for approximately 25 million patients across the United States, from 1998 to 2005.

#### Study Population

**Overall Economic Burden of DVT and PE**

For the analysis of the economic burden of DVT or PE, patients were included in the analysis if they had DVT and/or PE as the primary or secondary discharge diagnosis, and the hospitalization event occurred between February 1, 1998, and June 30, 2004. The first hospitalization for DVT or PE during the study period was defined as the index event. Patients were excluded if they did not have continuous health care plan enrollment and continuous pharmacy benefits for a minimum of 30 days prior to and 365 days following the hospitalization for DVT or PE. In addition, patients were excluded if they were aged older than 65 years and were not in the Medicare risk group (i.e., Medicare coverage with continuous pharmacy benefit from managed care organizations). Patient records that were not complete according to a prespecified list of required data fields, which included details of membership, hospitalization, outpatient medical, and outpatient pharmacy, were also excluded from the final analysis.

#### Comparison of Hospital Reimbursement of DVT/PE Readmissions

For the analysis of the economic burden of hospital readmission for DVT or PE, there were 2 additional criteria to ensure that these patients did have a true DVT or PE event and hospital readmission: (1) patients were required to have a minimum hospital length of stay of 3 days, and (2) patients were also required to have a minimum of 365 days where they did not have any DVT or PE hospitalization but had continuous health care plan enrollment prior to the index hospitalization (initial DVT or PE hospitalization).
**Data Collection and Analysis**

**Recurrent DVT or PE Analysis**

Demographic information was collected for all DVT and PE patients separately. To measure hospital readmission for DVT or PE, the following data were collected for primary or secondary diagnosis of DVT or PE: type of VTE event, time to first recurrent event, and time pattern of readmission (monthly percentages of readmission from the first month to 12 months after first discharge). Only reimbursed hospitalization costs were compared for both initial VTE admission and readmission. Outpatient medical and pharmacy costs were not measured and compared between the initial VTE admission and readmission, leading to patients being treated as outpatients in the emergency room not being included in the costs. In the evaluation of VTE hospital readmission rate, it was required that the initial DVT or PE hospital admission be followed by a DVT or PE hospital readmission within the required time period. In the evaluation of the time pattern of DVT or PE hospital readmission, only more specific readmission types are measured: an initial DVT admission followed by a DVT readmission or an initial PE admission followed by a PE readmission.

**Total Economic Burden of DVT or PE Analysis**

To measure the economic burden of VTE, the following data were collected separately for primary or secondary diagnosis of DVT or PE: type of VTE event, length of hospital stay, and average total annual reimbursement for DVT or PE-related inpatient costs, outpatient medical costs, outpatient procedure costs and outpatient pharmacy costs. In this analysis, VTE-related inpatient and outpatient pharmacy costs were defined as those incurred through use of a VTE treatment-related drug, namely unfractionated heparin (UFH), a low-molecular-weight heparin (LMWH: ardeparin, dalteparin, enoxaparin, or tinzaparin), or danaparoid, warfarin, or fondaparinux. VTE-related outpatient procedure costs were defined as those incurred through use of a VTE diagnosis and treatment-related procedures (Appendices A and B).

**Cost Calculations**

Costs associated with various measures of resource utilization were reported in the IHCIS database on the basis of actual reimbursement by the participating health care plans, and as such, only costs that were reimbursed by health care plans are included in this analysis. For inpatient professional services and outpatient services, only the cost associated with a DVT or PE diagnosis was used in the calculation. For outpatient lab procedures and prescription cost, only procedures or drugs related to the diagnosis and management of VTE were used in the cost calculation (Appendices A and B).

Patients with DVT or PE as secondary discharge diagnoses were matched by primary diagnosis, and only the portion of hospital facility cost that was attributable to DVT or PE was estimated and used for the total annualized health care cost. The DVT or PE attributable hospital facility cost is defined as the difference of hospital facility cost between the patient cohort with secondary diagnoses of DVT or PE and a control patient cohort.

For each member in the DVT or PE patient cohort, up to 3 non-DVT or non-PE members were selected from the database to form the control cohort based on the following matching criteria: same sex and geographical census region, ≤5-year age difference, and the same primary hospital discharge diagnosis (based on International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] codes).

Data and costs analysis were performed using SAS 8.2 software (SAS Institute Inc., Cary, NC). The Student's t test assuming unequal variances was carried out to test the statistical significance of the difference in the total hospitalization costs between DVT or PE readmission and the initial DVT or PE hospitalization. A P value below 0.05 was considered as statistically significant in this study.

**Results**

**Patient Population**

A total of 14,108 patients met the inclusion criteria of this study (Figure 1). Of these patients, 5,348 had a primary diagnosis of DVT in the index hospitalization, 2,984 had a primary diagnosis of PE, a further 5,776 patients had a secondary diagnosis of DVT and/or PE in the index hospitalization (4,593 DVT, 1,119 PE alone, and 64 DVT and PE).

Patients with a primary diagnosis were younger (mean age 53.9 years for the DVT-alone group and 52.7 for the PE-alone group) compared with patients with DVT or PE as a secondary diagnosis (mean age 55.5 and 54.6 years, respectively). Patients were predominantly female and came from a number of different census regions (Table 1).

**Hospital Readmission Rate for DVT or PE as Primary or Secondary Diagnosis**

In patients with a DVT or PE as the primary diagnosis, the rate of hospital readmission for DVT or PE over 1 year was 5.3%, while readmission was much higher in patients with DVT or PE as a secondary diagnosis, reaching a rate of 14.3% by 1 year (Figure 2). A clear trend of early occurrence was observed in patients with either DVT or PE as the primary diagnosis, with 27.1% of hospital readmissions for DVT and 44.3% of hospital readmissions for PE occurring in the first 30 days after the initial event (Figure 3A). A total of 50.7% of all hospital readmissions for DVT, and 58.6% of all hospital readmissions for PE had occurred within 90 days of the initial event. Similar trends were observed in patients with DVT or PE as a secondary diagnosis, with 22.8% and 46.4% of all hospital readmission for DVT having occurred at 30 and 90 days respectively, and 32.8% and 51.6% of all hospital readmission for PE having occurred at the same time points (Figure 3B).
Direct Medical Costs of Venous Thromboembolism and Subsequent Hospital Readmission Rates: An Administrative Claims Analysis From 30 Managed Care Organizations

**FIGURE 1** Study Population for the Determination of Overall Economic Burden of DVT or PE

- Hospitalizations in the IHCIS Database Between February 1, 1998, and June 30, 2004
  - (N = 5,030,349)
  - Excluding Hospitalizations Without DVT or PE as Discharge Diagnoses
    - (n = 4,971,997; 98.8%)
  - Hospitalizations With DVT or PE as Primary Discharge Diagnosis
    - (n = 32,193; 0.64%)
  - Hospitalizations With DVT or PE as Secondary Discharge Diagnosis
    - (n = 26,159; 0.52%)
  - Excluding DVT or PE as Primary Discharge Diagnosis Meeting Exclusion Criteria
    - (n = 23,861; 74.1%)
  - Excluding DVT or PE as Secondary Discharge Diagnosis Meeting Exclusion Criteria
    - (n = 20,383; 77.9%)
  - DVT or PE as Primary Discharge Diagnosis Not Meeting Exclusion Criteria
    - (n = 8,332; 25.9%)
  - DVT or PE as Secondary Discharge Diagnosis Not Meeting Exclusion Criteria
    - (n = 5,776; 22.1%)
  - Primary Diagnosis DVT
    - (n = 5,348; 64.2%)
  - Primary Diagnosis PE
    - (n = 2,984; 35.8%)
  - Secondary Diagnosis DVT
    - (n = 4,593; 79.5%)
  - Secondary Diagnosis PE
    - (n = 1,119; 19.4%)
  - Secondary Diagnosis DVT and PE
    - (n = 64; 1.1%)

* Discharge diagnosis determined with ICD-9 codes 451.1, 451.11, 451.19, 451.2, 451.9, 453.8, 453.9, 453.4, 453.40, 453.41, 453.42, 444.21, 444.81, 451.0, or 997.2 for DVT, and 415.1, 415.11, or 415.19 for PE.
† Exclusion criteria:
  * No continuous health care plan enrollment and continuous pharmacy benefit for a minimum of 30 days prior to, and 365 days following, the DVT or PE hospitalization.
  * Age ≥65 years and not in the Medicare risk group.
  * Incomplete patient records.

DVT = deep vein thrombosis; ICD-9 = International Classification of Diseases, Ninth Revision; PE = pulmonary embolism.
The Economic Burden of Hospital Readmission for DVT or PE

In patients with hospital readmission for a DVT or PE as primary diagnosis, the costs associated with the readmission were higher than the initial hospitalization (Figure 4). For patients with a DVT, total hospitalization cost was significantly greater by $2,057 (21%, from $9,805 to $11,862, \(P = 0.006\)), primarily due to an trend of increased length of hospital stay for the recurrent episode (from 7.7 to 8.7 days, \(P = 0.17\) [Appendix C]). For patients who had hospital readmission for PE, the total hospitalization cost for the readmission was $14,722 compared with $14,146 for the initial hospitalization (\(P = 0.38\)) [Appendix C]).

Resource Use and Economic Burden of VTE as the Primary Diagnosis

The average total annualized health care cost of a patient with a primary diagnosis of DVT or PE was $10,804 and $16,644, respectively (Table 2). The majority of the costs for both DVT and PE were hospitalization facility costs ($8,228 and $13,223 per patient, respectively), with hospitalization professional costs ($898 and $1,355 per patient) and outpatient procedure costs ($821 and $989 per patient) being the next most costly components. Resource utilization was also higher for PE patients than for DVT patients, with a longer average length of hospital stay (7.0 vs. 5.6 days), and higher numbers of outpatient prescriptions (7.5 vs. 6.4 prescriptions per patient), hospitalization professional service (10.7 vs. 7.6 services per patient), outpatient procedures (19.6 vs. 15.5 procedures per patient), and outpatient office visits (3.5 vs. 3.2 visits per patient) (Table 3).

Breakdown of Annual Cost of DVT and PE to Health Care Plans

The average annualized health care costs of DVT or PE were higher in the patients in the Medicare group than in the general population. In Medicare patients, the average costs for patients with a primary diagnosis of DVT or PE were $13,208 and $20,728 per patient, respectively, representing cost increases of $2,404 for DVT and $4,084 for PE over the whole population. The differences in costs were driven by increased hospital length of stay for the Medicare group. The higher costs in the...
Direct Medical Costs of Venous Thromboembolism and Subsequent Hospital Readmission Rates: An Administrative Claims Analysis From 30 Managed Care Organizations

Medicare group could be related to higher costs in patients aged ≥70 years. Although average costs were similar for age groups up to 70 years, they were approximately 25% higher in patients aged ≥70 years compared with the whole population (Table 4).

Economic Burden of DVT and PE as Secondary Diagnosis

The proportion of the average total annualized health care cost of a patient that was associated with a secondary diagnosis of DVT or PE was lower than in patients with a primary diagnosis at $7,594 and $13,018, respectively (Table 2). The cost in both the DVT and PE groups was primarily driven by hospitalization facility costs ($5,118 and $9,906, respectively), followed by hospitalization professional costs, outpatient procedure costs, and outpatient prescription costs. The cost of a patient having both DVT and PE in the secondary diagnosis was extremely high at $27,909. However, this result must be treated with caution since it was based on a low number of patients.

Discussion

In this study, utilizing actual health care plans reimbursement costs from approximately 25 million patients from across the United States in a large managed care database to estimate the costs associated with VTE, it was found that the annualized total health care costs of admission for a primary diagnosis of DVT or PE were $10,804 and $16,644, respectively. Furthermore, hospital readmission for DVT or PE occurred predominantly in the first 90 days following the initial event, with a high proportion of the readmissions occurring in the first 30 days following the initial event. DVT or PE readmissions were associated with an average total hospitalization cost per event of $11,862 for DVT and $14,722 for PE. The cost of hospital readmission for DVT was 21% greater than the cost for the initial DVT event, a difference driven by a trend toward an increased length of hospital stay (an average of 7.7 days for the initial admission vs. 8.7 days for the readmission \[P=0.17\]). A similar trend was not observed for patients who had an initial PE hospitalization.

The high rate of hospital readmission for DVT or PE found in the present study within the first 30 days or first 90 days is a point of concern for the quality of VTE care in hospitals, and is
in line with previous estimates. In a population-based cohort study of 1,719 patients with a first episode of DVT or PE, the cumulative percentage of patients with recurrent VTE was 5.2% at 30 days and 8.3% at 90 days. The cost per event of readmission for DVT and PE observed in our study was also similar to that seen in previous smaller study populations. In the cohort study of Bullano et al., a recurrent DVT or PE was associated with a total hospital cost of $11,419 and $11,014, respectively. These results highlight the importance of preventing a first episode of DVT or PE, in order to also reduce the cost burden associated with subsequent long-term complications.

The level of readmissions for VTE represents the “worst offenders” in readmission, since the patients are coming back for exactly the same disease that they just left the hospitals for, with a high proportion of readmission occurring in the first 30 days or first 90 days. This represents significant issues for the quality of care. The Joint Commission is in the process of developing a VTE prevention and care performance measurement initiative that will come out in 2008. The goal for individual hospitals will be to reduce the incidence of first episode DVT and PE, as well as the incidence of hospital readmissions for DVT or PE. The use of evidence-based, guideline-mandated prophylaxis and treatments may help to improve the continuum of care and reduce the economic burden of DVT and PE in these hospitals.

The costs of DVT and PE that were observed in patients with a primary diagnosis of DVT or PE were in line with the results seen in other smaller study populations. For example, in orthopedic surgery patients, the cost difference for the mean inpatient costs compared with patients without a VTE were $7,769 for those patients with a DVT and $9,176 with a PE. In a study comparing outpatient LMWH with inpatient unfractionated heparin for patients with confirmed DVT, the average inpatient cost of treating DVT was estimated to be $4,696 per hospitalization compared with $1,868 for outpatient treatment. However, in a retrospective analysis in a health maintenance organization in New Mexico, the total average cost for patients treated for a DVT in hospital with unfractionated heparin was $11,930. A study from 2 managed care organizations, in the southeastern and western United States, reported the total costs for more than 2,000 patients admitted to the hospital with a DVT or PE. It showed that the average cost per DVT event was $7,712 (median $3,131) and $9,566 (median $6,424) for a PE event.

Little data exists, however, on the total hospitalization cost of DVT or PE in large real-world studies that are representative of hospitals across the United States. The present study encompasses total annualized cost data from more than 12,000 patients with DVT or PE from across the United States, and the costs observed are higher than for many other studies. These higher costs compared with earlier studies may be a result of the data we used, including inpatient as well as outpatient payments to providers. Like Bullano et al., we used net payer costs (i.e., after subtraction of member cost), but we used outpatient costs that included pharmacy as well as inpatient hospital costs. We also report the costs associated with a secondary diagnosis of DVT or PE, providing an estimate of the relative component that a VTE event has in the total health care cost of patients presenting with comorbidities. MacDougall et al., in a similar analysis of administrative claims data for 1997 through the first quarter of 2004, found median annualized medical costs of $17,512 during and after the DVT event and $18,901 during and after the PE event, representing median annualized incremental costs compared with a prevent baseline of $10,285 for DVT patients and $12,520 for PE patients. These median costs are higher than the mean costs that we found in the present study, which may be explained in part by the inclusion of recurrent VTE in the main cost calculations of the previous study reported by MacDougall and colleagues.

Limitations

Foremost among the study limitations is the difficulty in isolating the incremental medical costs associated with VTE since these patients typically have multiple comorbid conditions. For example, Bullano et al. found previously that disease severity is high in these patients, including 59% with a history of or
Economic Burden of DVT and PE as Primary and Secondary Diagnosis, Average cost per Discharge Including 12 Months of Follow-up Period

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Total Cost ($)</th>
<th>Hospitalization Facility Cost ($)</th>
<th>Hospitalization Professional Cost ($) (VTE)</th>
<th>Outpatient Office Visit Cost ($) (VTE)</th>
<th>Outpatient Procedure Cost ($) (VTE)</th>
<th>Outpatient Prescription Cost ($) (VTE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DVT as primary diagnosis (n=5,348)</td>
<td>10,804</td>
<td>8,228 (76.2%)</td>
<td>898 (8.3%)</td>
<td>172 (1.6%)</td>
<td>821 (7.6%)</td>
<td>685 (6.3%)</td>
</tr>
<tr>
<td>DVT as secondary diagnosis (n=4,593)</td>
<td>7,594</td>
<td>5,118 (67.4%)</td>
<td>959 (12.6%)</td>
<td>107 (1.4%)</td>
<td>783 (10.3%)</td>
<td>628 (8.3%)</td>
</tr>
<tr>
<td>PE as primary diagnosis (n=2,984)</td>
<td>16,644</td>
<td>13,223 (79.4%)</td>
<td>1,355 (8.1%)</td>
<td>188 (1.1%)</td>
<td>989 (5.9%)</td>
<td>889 (5.3%)</td>
</tr>
<tr>
<td>PE as secondary diagnosis (n=1,119)</td>
<td>13,018</td>
<td>9,006 (76.1%)</td>
<td>1,276 (9.8%)</td>
<td>130 (1.0%)</td>
<td>900 (6.9%)</td>
<td>805 (6.2%)</td>
</tr>
<tr>
<td>DVT and PE as secondary diagnosis (n=64)</td>
<td>27,909</td>
<td>21,097 (75.6%)</td>
<td>2,538 (9.1%)</td>
<td>176 (0.6%)</td>
<td>1,823 (6.5%)</td>
<td>2,275 (8.2%)</td>
</tr>
</tbody>
</table>

DVT=deep vein thrombosis; PE=pulmonary embolism; VTE=venous thromboembolism.

Active malignancy. Second, the index event for patients in this study was hospitalization for either a primary or secondary diagnosis of DVT or PE, and as such, this study excludes patients who were seen in the emergency room, treated, and sent home on an LMWH or other anticoagulation. Therefore, this study would tend to overestimate the per-patient costs for VTE. On the other hand, since some patients with VTE treated in a hospital outpatient department were excluded, the incidence and prevalence of VTE would be underestimated by our methods.

Third, as with all retrospective administrative data analysis studies, there is the potential bias from missing data since some records are excluded from the analysis. However, since the sample size is large in the present study, and the missing data are not expected to be missing in a systematic manner, it is unlikely that this will have a large impact on the results. In the present study, we used a data source that did not disclose the plan names or detail information about the plans. There is, therefore, the chance that the results will not be representative of the national averages. We did however estimate the regional differences in the cost of primary DVT or PE (data not shown), and found that although differences did exist, they were not significant.

Fourth, in determining the inclusion and exclusion criteria of this study, a number of assumptions were made that may have impacted the results. We required patients to be enrolled in a health care plan before the DVT or PE event for a period of 30 days in the calculations of the total cost of DVT or PE, and for 365 days in the calculations of the hospitalization readmission costs.

Fifth, we also required that patients who were readmitted for DVT or PE had a minimum length of stay of 3 days in both the initial and readmission hospitalization. This was a conservative approach to ensure that during both the initial hospitalizations and readmissions, a minimum length of DVT or PE treatments were administered. However, many legitimate DVT or PE patients, such as those who were admitted for only 1 to 2 days and then discharged for outpatient LMWH treatments would have been excluded due to this conservative approach, leading to an overestimation of average cost, but an underestimation of total readmissions.

There are also a number of additional complications of DVT that were not investigated in this article, but which contribute to the total cost burden of the disease, such as post thrombotic syndrome (PTS). PTS was not included due to the fact that there is not universal consensus on using ICD-9-CM code +59.1 (postphlebitic syndrome) to represent PTS. The costs reported here are therefore likely to be an underestimate of the total long-term costs associated with a first DVT.

Conclusion

This study has demonstrated the high cost burden of DVT and PE among a large national managed care population. Furthermore, it shows that readmission for DVT or PE occurs in up to 14.3% of patients, with 27.1% to 44.3% of readmissions within 30 days, and 50.7% to 57.8% occurring within 90 days. Furthermore, DVT readmissions incur a 21% greater cost than the initial episode. Hospitals have the potential to reduce the national cost burden of VTE and meet new quality initiatives by ensuring that VTE events are prevented via the use of evidence-based, guideline-mandated prophylaxis options in patients identified at risk of VTE.

Acknowledgments

The authors acknowledge the valuable assistance of Essy Mozaffari, PharmD, MPH, sanofi-aventis, US, Inc., Bridgewater, New Jersey, in the design and implementation of the project and the preparation of the manuscript.
### TABLE 3  
Resource Utilization in 12 Months of Follow-up

<table>
<thead>
<tr>
<th></th>
<th>Total No. of Claims</th>
<th>Mean</th>
<th>SD</th>
<th>Median</th>
<th>IQR (Low)</th>
<th>IQR (High)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hospital admissions (LOS in days)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>DVT as primary diagnosis</td>
<td>6,101</td>
<td>5.6</td>
<td>6.0</td>
<td>4.0</td>
<td>3.0</td>
<td>6.0</td>
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<tr>
<td>DVT as secondary diagnosis</td>
<td>5,448</td>
<td>8.9</td>
<td>12.4</td>
<td>6.0</td>
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<td>10.0</td>
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<tr>
<td>PE as primary diagnosis</td>
<td>3,369</td>
<td>7.0</td>
<td>13.9</td>
<td>6.0</td>
<td>4.0</td>
<td>8.0</td>
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<td>14.0</td>
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<td>DVT and PE as secondary diagnosis</td>
<td>185</td>
<td>16.8</td>
<td>16.9</td>
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<td>18.0</td>
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<td><strong>Hospital inpatient professional service</strong></td>
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<td>DVT and PE as secondary diagnosis</td>
<td>1,194</td>
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<td><strong>Physician office visits</strong></td>
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<td>29.0</td>
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<td>36.0</td>
<td>7.0</td>
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<td>31.0</td>
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<td><strong>Outpatient prescriptions</strong></td>
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<td>5.4</td>
<td>6.0</td>
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<td>10.0</td>
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<td>6.5</td>
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<td>4.0</td>
<td>11.0</td>
</tr>
</tbody>
</table>

* Average use per patient, e.g., number of outpatient office visits per patient. Only resources and treatments used for treatment of a DVT or PE diagnosis are included (see Appendix B).

DVT = deep vein thrombosis; IQR = interquartile range; LOS = length of hospital stay; PE = pulmonary embolism.

**DISCLOSURES**

Financial and editorial support for this research was provided by sanofi-aventis and was obtained by author Alex C. Spyropoulos, who is a paid consultant to sanofi-aventis; author Jay Lin is an employee of sanofi-aventis. Spyropoulos served as principal author of the study. Study concept and design, data collection and interpretation, and writing of the manuscript and its revision were the work of both authors.

**REFERENCES**

Direct Medical Costs of Venous Thromboembolism and Subsequent Hospital Readmission Rates: An Administrative Claims Analysis From 30 Managed Care Organizations

<table>
<thead>
<tr>
<th>TABLE 4</th>
<th>Average Cost per Discharge for DVT or PE as Primary Diagnosis With Breakdown by Age Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Years)</td>
<td>DVT as Primary Diagnosis</td>
</tr>
<tr>
<td>n (%)</td>
<td>Hospitalization Costs ($)</td>
</tr>
<tr>
<td>&lt;40</td>
<td>919 (17.2)</td>
</tr>
<tr>
<td>40-49</td>
<td>1,170 (21.9)</td>
</tr>
<tr>
<td>50-59</td>
<td>1,611 (30.1)</td>
</tr>
<tr>
<td>60-69</td>
<td>911 (17.0)</td>
</tr>
<tr>
<td>≥70</td>
<td>737 (13.8)</td>
</tr>
<tr>
<td>Total/average</td>
<td>5,348</td>
</tr>
</tbody>
</table>

DVT=deep vein thrombosis, PE=pulmonary embolism.

### Direct Medical Costs of Venous Thromboembolism and Subsequent Hospital Readmission Rates: An Administrative Claims Analysis From 30 Managed Care Organizations

### APPENDIX A Imaging and Laboratory Procedures of Interest

<table>
<thead>
<tr>
<th>CPT-4 Codes</th>
<th>Description</th>
<th>Imaging Services</th>
</tr>
</thead>
<tbody>
<tr>
<td>36488-36491, 36493</td>
<td>Central venous catheter (placement and repositioning)</td>
<td>85210 Factor II, activity*</td>
</tr>
<tr>
<td>71010-71035</td>
<td>Chest radiography</td>
<td>85220 Factor V, activity*</td>
</tr>
<tr>
<td>71040-71060</td>
<td>Bronchography</td>
<td>85230 Factor VII, activity*</td>
</tr>
<tr>
<td>71275</td>
<td>Computed tomographic angiography, chest</td>
<td>85240 Factor VIII, activity*</td>
</tr>
<tr>
<td>71550-71555</td>
<td>Magnetic resonance imaging, chest</td>
<td>85244 Factor VIII antigen*</td>
</tr>
<tr>
<td>75741-75746</td>
<td>Pulmonary angiography*</td>
<td>85245 Ristocetin cofactor*</td>
</tr>
<tr>
<td>76880, 76856-76857</td>
<td>Ultrasonography</td>
<td>85246 Von Willebrand antigen*</td>
</tr>
<tr>
<td>78580-78594</td>
<td>Venous thrombosis imaging*</td>
<td>85247 Von Willebrand factor multimers*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CPT-4 Codes</th>
<th>Description</th>
<th>Laboratory Services</th>
</tr>
</thead>
<tbody>
<tr>
<td>75820-75827</td>
<td>Venography, extremity, caval*</td>
<td>85250 Factor IX, activity*</td>
</tr>
<tr>
<td>75831-75872</td>
<td>Venography, renal, adrenal, neuro</td>
<td>85260 Factor X, activity*</td>
</tr>
<tr>
<td>78457, 78458</td>
<td>Venous thrombosis imaging*</td>
<td>85270 Factor XI, activity*</td>
</tr>
<tr>
<td>78580-78594</td>
<td>Ventilation/perfusion lung scan</td>
<td>85280 Factor XII, activity*</td>
</tr>
<tr>
<td>78596</td>
<td>Ventilation/perfusion study*</td>
<td>85290 Factor XIII, activity*</td>
</tr>
<tr>
<td>93875</td>
<td>Noninvasive study of extracranial arteries (bilateral)</td>
<td>85291 Factor XIII, solubility*</td>
</tr>
<tr>
<td>93880-93882</td>
<td>Duplex/unilateral scan of extracranial arteries</td>
<td>85292 Prekallikrein assay*</td>
</tr>
<tr>
<td>93886-93888</td>
<td>Transcranial Doppler study of intracranial arteries (limited or complete)</td>
<td>85293 HMW kininogen*</td>
</tr>
<tr>
<td>93922-93924</td>
<td>Noninvasive physiologic studies upper/lower extremity arteries including Doppler waveform analysis</td>
<td>85300 Clotting inhibitors, antithrombin III, activity*</td>
</tr>
<tr>
<td>93925-93931</td>
<td>Duplex scan of upper/lower extremities</td>
<td>85301 Antithrombin III, antigen assay*</td>
</tr>
<tr>
<td>93965</td>
<td>Doppler Continuous-wave ultrasound; plethysmography*</td>
<td>85302 Protein C, antigen*</td>
</tr>
<tr>
<td>93970-93971</td>
<td>Compression ultrasound of extremity veins*</td>
<td>85303 Protein C, activity*</td>
</tr>
<tr>
<td>93990</td>
<td>Extremity arterial-venous studies; duplex scan of hemodialysis access</td>
<td>85305 Protein S, total*</td>
</tr>
<tr>
<td>93978-85380</td>
<td>Fibrin degradation products, D-dimer*</td>
<td>85306 Protein S, free*</td>
</tr>
</tbody>
</table>

* Events are included as outpatient disease-related resource utilization and costs.

CPT=Current Procedural Terminology
**APPENDIX B**

ICD-9 Codes Used for DVT or PE Diagnosis

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>451.1</td>
<td>Phlebitis &amp; thrombophlebitis deep veins lower extremity</td>
</tr>
<tr>
<td>451.11</td>
<td>Phlebitis and thrombophlebitis of femoral vein</td>
</tr>
<tr>
<td>451.19</td>
<td>Phlebitis &amp; thrombophlebitis of deep vessels lower extremity</td>
</tr>
<tr>
<td>451.2</td>
<td>Phlebitis &amp; thrombophlebitis lower extremity unspecified</td>
</tr>
<tr>
<td>451.9</td>
<td>Phlebitis &amp; thrombophlebitis of unspecified site</td>
</tr>
<tr>
<td>453.8</td>
<td>Embolism &amp; thrombosis of other specified veins</td>
</tr>
<tr>
<td>453.9</td>
<td>Embolism &amp; thrombosis of unspecified site</td>
</tr>
<tr>
<td>453.4</td>
<td>Venous embolism &amp; thrombosis deep vessels lower extremity</td>
</tr>
<tr>
<td>453.40</td>
<td>Venous embolism &amp; thrombosis uns deep vessels lower extremity</td>
</tr>
<tr>
<td>453.41</td>
<td>Venous embolism &amp; thrombosis deep vessels prox lower extremity</td>
</tr>
<tr>
<td>453.42</td>
<td>Venous embolism &amp; thrombosis deep vessels dist lower extremity</td>
</tr>
<tr>
<td>444.21</td>
<td>Embolism &amp; thrombosis arteries upper extremity</td>
</tr>
<tr>
<td>444.81</td>
<td>Embolism &amp; thrombosis of iliac artery</td>
</tr>
<tr>
<td>451.0</td>
<td>Phlebitis &amp; thrombophlebitis sup vessels lower extremity</td>
</tr>
<tr>
<td>997.2</td>
<td>Peripheral vascular complications nec</td>
</tr>
</tbody>
</table>

**APPENDIX C**

Hospital Length of Stay in Discharges During Initial Hospitalization or Readmission* for DVT or PE

<table>
<thead>
<tr>
<th>Discharge Group</th>
<th>Length of Stay (Days)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>First DVT admission</td>
<td>7.7</td>
<td></td>
</tr>
<tr>
<td>DVT readmission</td>
<td>8.7</td>
<td>0.17</td>
</tr>
<tr>
<td>First PE admission</td>
<td>7.4</td>
<td></td>
</tr>
<tr>
<td>PE readmission</td>
<td>7.6</td>
<td>0.38</td>
</tr>
</tbody>
</table>

*Readmissions with hospital stay less than 3 days were excluded.

**APPENDIX D**

Comorbidities in Patients With DVT and PE

<table>
<thead>
<tr>
<th>Comorbidity Categories</th>
<th>1° DVT (%)</th>
<th>2° DVT (%)</th>
<th>1° PE (%)</th>
<th>2° PE (%)</th>
<th>2° DVT + PE (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infectious and parasitic diseases</td>
<td>1.6</td>
<td>1.0</td>
<td>1.5</td>
<td>1.0</td>
<td>0.7</td>
</tr>
<tr>
<td>Neoplasms</td>
<td>6.4</td>
<td>4.1</td>
<td>5.0</td>
<td>3.4</td>
<td>4.9</td>
</tr>
<tr>
<td>Endocrine, nutritional, metabolic, immunity</td>
<td>13.9</td>
<td>8.8</td>
<td>12.0</td>
<td>8.2</td>
<td>7.3</td>
</tr>
<tr>
<td>Blood and blood-forming organs</td>
<td>5.9</td>
<td>3.7</td>
<td>4.5</td>
<td>3.0</td>
<td>4.8</td>
</tr>
<tr>
<td>Mental disorders</td>
<td>5.5</td>
<td>3.5</td>
<td>4.5</td>
<td>3.0</td>
<td>2.9</td>
</tr>
<tr>
<td>Nervous system and sense organs</td>
<td>2.5</td>
<td>1.6</td>
<td>1.9</td>
<td>1.3</td>
<td>1.6</td>
</tr>
<tr>
<td>Circulatory system</td>
<td>31.2</td>
<td>53.6</td>
<td>34.1</td>
<td>55.2</td>
<td>56.6</td>
</tr>
<tr>
<td>Respiratory system</td>
<td>5.6</td>
<td>3.5</td>
<td>13.0</td>
<td>8.8</td>
<td>6.2</td>
</tr>
<tr>
<td>Digestive system</td>
<td>5.0</td>
<td>3.2</td>
<td>4.9</td>
<td>3.3</td>
<td>2.7</td>
</tr>
<tr>
<td>Genitourinary system</td>
<td>4.1</td>
<td>2.6</td>
<td>3.8</td>
<td>2.6</td>
<td>3.3</td>
</tr>
<tr>
<td>Complications of pregnancy, childbirth, puerperium</td>
<td>0.1</td>
<td>0.1</td>
<td>0.2</td>
<td>0.1</td>
<td>0.0</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue</td>
<td>4.0</td>
<td>2.5</td>
<td>1.1</td>
<td>0.7</td>
<td>1.0</td>
</tr>
<tr>
<td>Musculoskeletal system and connective tissue</td>
<td>5.0</td>
<td>3.2</td>
<td>3.2</td>
<td>2.2</td>
<td>2.6</td>
</tr>
<tr>
<td>Congenital anomalies</td>
<td>0.4</td>
<td>0.3</td>
<td>0.4</td>
<td>0.3</td>
<td>0.1</td>
</tr>
<tr>
<td>Conditions in the perinatal period</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Symptoms, signs, and ill-defined conditions</td>
<td>5.8</td>
<td>3.7</td>
<td>7.4</td>
<td>5.0</td>
<td>3.8</td>
</tr>
<tr>
<td>Injury and poisoning</td>
<td>2.8</td>
<td>4.6</td>
<td>2.6</td>
<td>1.8</td>
<td>1.6</td>
</tr>
</tbody>
</table>

DVT=deep vein thrombosis, PE=pulmonary embolism.
Analysis of Factors Associated With Statin Adherence in a Hierarchical Model Considering Physician, Pharmacy, Patient, and Prescription Characteristics

Alexander Pedan, PhD; Laleh T. Varasteh, RPh, MSF; and Sebastian Schneeweiss, MD, ScD

ABSTRACT

BACKGROUND: Adherence with maintenance drug therapy such as HMG-CoA reductase inhibitors (statins) is typically analyzed from the perspective of patient characteristics.

OBJECTIVE: To determine the effects of physician and pharmacy characteristics in addition to patient characteristics on variation in adherence rates for 4 statin drugs (atorvastatin, pravastatin, rosuvastatin, and simvastatin) for patients who patronized only 1 pharmacy and 1 prescriber of a statin.

METHODS: A retrospective cohort study of 6,436 patients who initiated statin therapy was performed from computerized pharmacy records of 2 large national pharmacy chains. Adherence was defined as the number of 30-day prescription refills within 12 months after initiation of statin therapy. Physician, pharmacy, prescription, and patient covariates were considered in a cross-classified hierarchical regression model.

RESULTS: The average number of refills dispensed was 4.75 per patient. Patients younger than 50 years had, on average, 13.6% fewer refills per year than did patients older than 70 years (P<0.001). Women were 4.4% less adherent than men (P=0.041). Patients residing in southern states were significantly less adherent than were other patients; they had 19.4% fewer refills per year than did patients from western states (P<0.001). Each prescription dispensed for comorbid conditions increased adherence by 2.0% (P=0.002), and patients with a history of cardiovascular drug use were 14.1% more adherent than were other patients (P<0.001). Patients on a higher statin dose appeared to be 8.4% less adherent than were patients on a lower dose (P<0.001). Adherence was greater as the number of prescribed refills increased, with a rate of 2.1% per refill (P<0.001). Adherence was lower for patients with higher copayments, with a rate of 2.2% per each additional $10 of copayment (P<0.001). For patients treated by physicians in the top 2.5 percentile and bottom 2.5 percentile of statin adherence, mean refill counts per year were 6.1 and 2.9, respectively. For patients on a higher statin dose, mean refill counts per year were 6.6 and 2.5, respectively. Adherence increased at a rate of 28.4% per each additional 100 statin patients per pharmacy (P<0.001) and decreased at a rate of about 6.5% per each additional 10 statin patients per treating physician (P<0.001).

CONCLUSION: Because of the variability in adherence rates across pharmacies and physicians, further assessment of pharmacy and physician characteristics in addition to patient characteristics may be of value in improving adherence.

KEYWORDS: Adherence, Variation, Hierarchical model, Statins, Persistence

What is already known about this subject

• To our knowledge, this study is the first attempt to assess the amount of variation in adherence that can be attributed separately to physicians and pharmacies, after adjusting for patient case mix.

• Adherence was greater as the number of statin patients using a particular pharmacy increased, at a rate of 28.4% per each additional 100 statin patients per pharmacy. A significant inverse relationship was observed between the number of statin patients treated by a given physician and adherence: adherence decreased at a rate of about 6.5% per each additional 10 statin patients per physician.

• For patients who patronized pharmacies in the top 2.5 percentile and bottom 2.5 percentile of statin adherence, mean refill counts per year were 6.1 and 2.9, respectively. For patients treated by physicians in the top 2.5 percentile and bottom 2.5 percentile of statin adherence, mean refill counts per year were 6.6 and 2.5, respectively.

What this study adds

• To date, most studies of adherence have studied only the effects of patient characteristics on patient adherence. Few studies have examined how much of a variability in patient adherence outcome is attributed to an individual physician, and no studies have been published on how much is attributed to an individual pharmacy.

There are many efficacious medications available today to treat and prevent conditions of considerable morbidity and mortality. However, in the majority of cases, treatment success is suboptimal. The most common reason for treatment failure is lack of adherence to the prescribed drug therapy. In general, fewer than 50% of patients receiving long-term treatment adequately adhere to their prescribed regimens, regardless of their disease state.1-3 A low level of medication adherence for conditions such as diabetes, hypertension, hypercholesterolemia, and congestive heart failure is associated with a higher level of disease-related medical costs.9
For medications that prevent future morbidity, such as lipid-lowering and antihypertensive drugs, it has been particularly difficult to achieve high levels of adherence. The efficacy of lipid-lowering therapy in reducing the burden of coronary heart disease (CHD), the leading cause of death in the United States, is well established. \(^5\)\(^-\)\(^9\) HMG-CoA reductase inhibitors (statins) can significantly reduce the incidence of CHD and mortality from acute myocardial infarction. However, adherence to statin regimens is critical for the successful prevention of CHD. The majority of patients for whom statins are prescribed in routine clinical practice either stop taking the drug altogether or take less than the prescribed dose. Cohort studies of patients who were prescribed statins show variable and often high rates of therapy discontinuation. \(^10\)\(^-\)\(^12\) Simons et al. reported that only about 50% of patients who were prescribed a lipid-lowering drug were still taking it 6 months later. \(^13\) The percentage of adherent patients dropped to 30% to 40% after 12 months. \(^13\)\(^,\)^ \(^14\)

There are many barriers to adherence, including lack of education, cost of treatment, low physician trust, side effects, inadequate provider-patient communication, and convenience factors. \(^15\)\(^-\)\(^17\) No standard strategy exists for improving adherence. Several comprehensive pharmacy care programs have been used that have improved patient adherence and outcomes. A new multiphase study published by Lee and colleagues tested medication adherence in community-based patients aged 65 years and older who received usual care compared with continued pharmacy care (standardized medication education, regular follow-up by pharmacists, and medications dispensed in a time-specific manner). This intervention improved medication adherence and persistence and resulted in meaningful clinical reductions in blood pressure; discontinuation of the program resulted in lower medication adherence and persistence. \(^15\)

Other clinical studies have also shown a positive impact on patient medication adherence. Project ImPACT took place at 26 community-based ambulatory care pharmacies. As part of the triangle of care (patient, pharmacist, and physician), pharmacists actively educated patients about the risks associated with high cholesterol levels, the importance of controlling their cholesterol levels, and treatment goals. Pharmacists also conferred with physicians on the type of medication needed for each patient. This study demonstrated that clear communication and collaboration between patients, pharmacists, and physicians could result in improved adherence, enabling patients to reach their treatment goal. \(^18\)

Other studies have shown that poor relationships and/or poor communication between patient and physician can lead to low rates of adherence. Piette and colleagues examined the role of patient-physician trust in medication adherence. They found that when physician trust levels were low, patients were more likely to forgo medication treatment. \(^16\) Young and colleagues assessed physician information-giving habits across internists and family physicians prescribing antidepressants. The results showed that physicians provided limited information to patients and frequently did not discuss information critical to improving adherence to therapy. \(^19\)

One of the challenges for planning effective interventions to improve medication adherence is to identify the weakest element in the chain from prescribing to persistent use by patients. If such targets for intervention can be identified, then relatively expensive programs developed to improve adherence can become more cost-effective. Strategies and interventions to improve adherence on the individual patient level are highly variable and include adherence aids, refill or follow-up reminders, regimen simplification, various subsidies such as coupons and rebates, written and oral education, and comprehensive medication and disease management. \(^19\) Aside from patients, physicians and pharmacies are potential intervention targets. The main objective of our analysis is to assess the relative importance of pharmacies and physicians on the variation in patient adherence to statin therapy. An additional goal is to examine the effects of patient-, prescription-, and provider-level characteristics on statin adherence.

**Methods**

**Patients**

A retrospective cohort study was performed for patients who initiated statin therapy. The data for this study were obtained from blinded computerized pharmacy prescription records of 2 national pharmacy chains representing more than 4,300 community pharmacies nationwide. Data contained prescription drug activity for all prescriptions filled at these national chains for each individual patient, regardless of health care plan. Patients were selected on the basis of the presence of an initial prescription for atorvastatin, rosuvastatin, pravastatin, or
Analysis of Factors Associated With Statin Adherence in a Hierarchical Model Considering Physician, Pharmacy, Patient, and Prescription Characteristics

Simvastatin between August 1, 2004, and September 30, 2004 (Figure 1). Other statins (i.e., fluvastatin, generic lovastatin, and simvastatin with ezetimibe) constituted less than 3% of all statin prescriptions and were not included in the analysis because of the low volume.

The date of the first statin dispensing during the study period was the index date of the analysis. Only patients who had no statin dispensed in the 6 months before the index date in the same pharmacy chain were included in the study (Figure 2). The analysis was restricted to include index prescriptions with only a 30-day supply to avoid misclassifying adherence by ensuring that all study patients had an equivalent starting point. (Patients with less than a 30-day supply for the index script would have, on average, more refills than would patients with a 30-day supply, making these patients erroneously look more adherent. Conversely, patients with more than a 30-day supply for the index script would have, on average, fewer refills than would patients with a 30-day supply, making these patients erroneously look less adherent.)

Patients who filled statin prescriptions written by more than 1 physician or who patronized more than 1 pharmacy within a chain were excluded from the analysis. Patient adherence was evaluated for 1 year after the index date. The analysis was further restricted to physicians and pharmacies who represented at least 4 patients eligible for our analysis during the study period to allow for more stable multilevel estimates.

All patient identifiers were deleted after linkage, and nontraceable study ID numbers were assigned. This study was approved by the Institutional Review Board of Brigham and Women’s Hospital.

Adherence Outcome

Rates of refilling prescriptions are often used as an accurate and objective measure of overall prescription drug adherence. Since statin therapy is chronic in nature, we assumed that any completed prescription (i.e., new prescription plus all authorized refills) was going to be followed by a new prescription. The outcome variable was defined as the total number of 30-day refills that patients obtained during the 1-year follow-up period.

All analyses were performed at the patient level; all statin fills for each patient were summed even if they represented new prescription numbers or switches from one statin to another. Few patients (approximately 4%), however, switched to another statin during the study evaluation period.

About 4.1% of all patients selected for the analysis received the first prescription with a 30-day supply and then the following prescription(s) with a 60- or 90-day supply. For these patients, we created a proxy of 30-day refills, counting, for example, a refill with a 60- or 90-day supply as 2 or 3 refills with a 30-day supply. Patients with 11 or more refills were considered fully adherent.

FIGURE 2 Flowchart of Statin Patient Selection

Covariates

The measured patient-level characteristics included age, gender, number of existing comorbid conditions (measured using a count of Chronic Disease Score [CDS] disease categories), history of cardiovascular diseases (measured using the cardiovascular component of the CDS), region of residence (Northeast, Midwest, South, and West), and index prescription-specific characteristics (daily dose, number of refills prescribed, and copayment). Patients’ baseline comorbid conditions and history of cardiovascular diseases were identified from prescriptions filled during the 6-month period before the index date. The daily doses were grouped into high and low categories, where the low-dose category included patients with the prescribed daily doses of 10 mg or less for atorvastatin and simvastatin, 5 mg or less for rosuvastatin, and 20 mg or less for pravastatin. Physician-and pharmacy-level characteristics consisted of the total number of patients treated with lipid-lowering drugs in the enrollment period and pharmacy chain indicators.
Statistical Analysis Using Hierarchical Models

Patient, physician, and pharmacy characteristics are all important factors affecting patient-level adherence outcomes. Traditional multivariate techniques treat observations as though they were independent. However, patients in a given physician practice or pharmacy may share characteristics, and their outcomes are unlikely to be truly independent of one another. For example, a physician may tailor his/her clinical practice toward specific diseases and/or socioeconomic subgroups. At the pharmacy level, the pharmacy location, size, daily prescription volume, number of pharmacists, degree of counseling, etc., may result in less heterogeneity in the patient population. Patients associated with a physician or with a pharmacy form a natural 2-level hierarchical structure. Ignoring the clustering that exists in hierarchical data may result in a biased estimation of both parameter estimates and their variances, and therefore will result in a false statistical inference.

A statistical technique that is well suited to explore the effects of pharmacy and physician characteristics on patient adherence is multilevel modeling or random effects regression models.24-27 Additional hierarchical levels can be easily added to the model. The 2-level hierarchy of physicians and patients (1 physician sees several patients) could be expanded to include pharmacies at a third level. However, no clear hierarchy can be defined between physicians and pharmacies because patients can fill prescriptions at different pharmacies. Conversely, customers of a specific pharmacy are treated by many different physicians. In this situation, patients are said to be contained within cross-classification of physicians by pharmacies.26

We will denote by $Y_{ij}$ the adherence outcome for patient $i$, treated by physician $j$, and filling prescriptions at pharmacy $j_2$, and the corresponding expected value is denoted as $E(Y_{ij})$. The adherence outcome is the count of 30-day refills in 12 months. The standard distribution for counts is the Poisson distribution. However, in real-life applications, variability among counts is usually greater than would be expected by simple Poisson distribution. Such extra variability is called overdispersion. The negative binomial regression is the generalization of the Poisson regression, which takes into account the possibility of overdispersion. To account for possible overdispersion, the adherence outcome was modeled with a negative binomial distribution.28,29

One of the important features of negative binomial distributions is that the variance is not a free parameter as in the case of a normal distribution, but is a function of the mean. In terms of hierarchical modeling, this leads to a relationship between the parameters in the fixed part of the model and the parameters of the random part.26 To answer the question of how much variability in the patient’s adherence outcome is attributable to the process occurring at the pharmacy level than at the physician level, we will consider the following cross-classified negative binomial hierarchical model:

$$Y_{ij} \sim \text{NB}(\mu_{ij}, \phi),$$

$$\log(\mu_{ij}) = (X\beta)_{ij} + u_i + u_{ij},$$

$$u_i \sim N(0, \sigma_u^2),$$

$$u_{ij} \sim N(0, \sigma_{u_{ij}}^2),$$

where $(X\beta)_{ij}$ is the set of linear predictors and parameters $u_i$ and $u_{ij}$ represent the physician-specific and pharmacy-specific contributions to patient adherence.

Here we model the negative binomial variation at the patient level and assume that variations at physician and pharmacy levels are independent and normally distributed with means of 0 and variances of $\sigma_u^2$ and $\sigma_{u_{ij}}^2$, respectively. The log-linear nature of this regression means that the independent predictors $(X\beta)_{ij}$ and the level-2 random parameters $u_i$ and $u_{ij}$ have multiplicative effects on the expected counts of refills. For example, if there is only 1 explanatory variable $X_1$, the right side of the above equation is equivalent to $\exp(\beta_1) \exp(u_i) \exp(u_{ij})$, where $\beta_1$ is the intercept. Therefore, each additional unit of $X_1$ will have the effect of multiplying the expected number of refills by $\exp(\beta_1)$.

Similarly, in a pharmacy with a high intercept, for example, 2 standard deviations, so that $u_p=2\sigma_u$, the expected number of refills will be $\exp(2\sigma_u)$ times as high as in a pharmacy with the average value, $u_p = 0$, of the intercept.35 Another consequence of multiplicity of effects is that no simple relationship exists between the variance of an outcome and the variances of the random effects.26

The significance of the fixed parameters is evaluated using 2-sided $t$ tests. The interactions between different covariates were checked and found to be nonsignificant at the $\alpha = 0.1$ level. Accordingly, the final multivariate model included only main effects. The significance of the random parameters is evaluated by the Wald test, comparing the estimates divided by their standard errors with a standard normal distribution. Because the variance components are bounded by 0, the null hypotheses of no variance ($H_0: \sigma_{u_{ij}}^2 = 0$, $k=1, 2$) are tested against the 1-sided alternative hypotheses ($H_1: \sigma_{u_{ij}}^2 > 0$, $k=1, 2$).

Parameter estimation in the above hierarchical generalized linear model is done by restricted pseudo-likelihood methods as implemented in the SAS GLIMMIX procedure (SAS v. 9.13, Cary, NC).30

**Results**

The final cohort consisted of 6,436 patients initiating statin therapy at 586 pharmacies prescribed by 1,059 physicians. Table 1 lists baseline patient and prescription characteristics. The average age of the patients was 59.9 years (SD = 13.1, range 8-101) and 49.8% were female. The mean statin copayment for the index prescription was $28.64 (SD = $32.67, range $0-$377.50). Patients had, on average, 2.0 (SD = 2.0, range 0-12) prescriptions dispensed for comorbid conditions (defined by CDS categories); more than 27% of patients had no prescrip-
Analysis of Factors Associated With Statin Adherence in a Hierarchical Model Considering Physician, Pharmacy, Patient, and Prescription Characteristics

Table 1: Characteristics of 6,436 Patients at the Time of the Index Statin Prescription

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Characteristic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>History of cardiovascular drug use†</td>
</tr>
<tr>
<td>Mean [SD]</td>
<td>Pharmacy chain</td>
</tr>
<tr>
<td>≤50</td>
<td>A</td>
</tr>
<tr>
<td>51-60</td>
<td>B</td>
</tr>
<tr>
<td>61-70</td>
<td>No. of prescriptions dispensed for comorbid conditions</td>
</tr>
<tr>
<td>&gt;70</td>
<td>Mean [SD]</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td></td>
</tr>
<tr>
<td>Region of residence*</td>
<td></td>
</tr>
<tr>
<td>Northeast</td>
<td></td>
</tr>
<tr>
<td>Midwest</td>
<td></td>
</tr>
<tr>
<td>South</td>
<td></td>
</tr>
<tr>
<td>West</td>
<td></td>
</tr>
<tr>
<td>Index dose of statin drug‡</td>
<td></td>
</tr>
<tr>
<td>High dose</td>
<td></td>
</tr>
<tr>
<td>Low dose</td>
<td></td>
</tr>
<tr>
<td>Index prescription copayment</td>
<td></td>
</tr>
<tr>
<td>Mean [SD]</td>
<td></td>
</tr>
<tr>
<td>&lt;$1</td>
<td></td>
</tr>
<tr>
<td>$1.10-$10</td>
<td></td>
</tr>
<tr>
<td>$10.10-$50</td>
<td></td>
</tr>
<tr>
<td>&gt;$50</td>
<td></td>
</tr>
</tbody>
</table>

* Northeast states: CT, MA, ME, NH, NJ, NY, PA, RI, and VT; midwest states: IA, IL, IN, KS, MI, MN, MO, ND, NE, OH, SD, and WI; southern state: AL, AR, DE, FL, GA, KY, LA, MD, MS, NC, OK, SC, TN, TX, VA, WV, and Washington DC; western states: AK, AZ, CA, CO, HI, ID, MT, NM, NV, OR, UT, WA, and WY.
† Used during 6 months prior to the index date. Drug groups 31-40, defined by Medi-Span Generic Product Indicator (GPI) therapeutic classification system.
‡ Prescriptions were grouped into high and low categories, where the low-dose category was defined as a daily dose 10 mg or less for atorvastatin and simvastatin, 5 mg or less for rosvastatin, and 20 mg or less for pravastatin.
§ PRN (as-needed) refills were coded as 12 refills prescribed.

Table 2 shows results of the cross-classified multivariate hierarchical regression model of patient adherence to statin therapy. Based on the significance level, adherence was most strongly associated with the number of refills prescribed and copayment for the index prescription. Patients and index prescription characteristics that are significantly associated with adherence included age, gender, region of residence, index copayment, index dose, number of prescriptions dispensed for comorbid conditions, and prior history of cardiovascular disease. As discussed earlier, the effect of each predictor on patient adherence can be quantified by exponentiation of parameter estimates from Table 2, exp(β). On the basis of these calculations, we can conclude that patients younger than
50 years had, on average, 13.6% fewer refills per year (exp(β)=0.864) than did patients older than 70 years (P<0.001). Women were 4.4% less adherent than were men (P = 0.041). Patients residing in southern states had 19.4% fewer refills per year than did patients from western states (P <0.001). Each comorbid condition increased adherence by 2.0% (P = 0.002) and patients with a history of cardiovascular drug use were 14.1% more adherent than were other patients (P <0.001). Patients on a higher statin dose appeared to be 8.4% less adherent than were patients on a lower statin dose (P<0.001). Adherence was greater as the number of prescribed refills increased, with a rate of 2.1% per refill prescribed (P<0.001). Adherence was lower for patients with a higher copayment, at a rate of 2.2% per each additional $10 of copayment (P<0.001).

At the second level of our hierarchical structure, adherence was greater, as the number of statin patients using a particular pharmacy increased, with a rate of 28.4% per each additional 10 statin patients per pharmacy (P <0.001). Also, a significant inverse relationship was observed between the number of statin patients treated by a given physician and adherence: adherence decreased at a rate of about 6.5% per each additional 10 statin patients per physician (P <0.001).

The physician- (σ_u^2) and pharmacy-level (σ_v^2) variance components (and their standard errors) yield the following estimates of 0.021 (0.007) and 0.035 (0.007), respectively, indicating a slightly more variability across pharmacies than across physicians with respect to patient adherence to statin therapy. The variances at both physician and pharmacy levels are highly statistically significant. As mentioned earlier, random effect parameters have a multiplicative effect on the expected counts of refills. Particularly, each expected count of refills is multiplied by \( \exp(u_j) \) to account for the effect of specific physician and by \( \exp(u_j) \) to account for the effect of specific pharmacy (with these multipliers equal to 1 for average values of \( u_j = 0 \) and \( u_j = 0 \)).

Under the assumption of normality of random effects, we would expect that patients at 2.5% of all pharmacies had at least \( e^{1.96\sqrt{0.021}} = 1.45 \) more refills than did the conditional average (defined by case mix), and that patients at 2.5% of all pharmacies had at least \( 1.45 (e^{1.96\sqrt{0.021}}) \) fewer refills than did the conditional average. Therefore, we can say that patients at the upper (best) 2.5% of all pharmacies have, on average, at least 2 (1.45 \( e^{1.96\sqrt{0.021}} \)) times more statin refills than do patients at the lower (worst) 2.5% of all pharmacies. Similar calculations show that patients at the upper (best) 2.5% of all physicians have, on average, at least 1.75 times more statin refills than do patients at the lower (worst) 2.5% of all physicians.

For patients who patronized pharmacies in the top 2.5 percentile and bottom 2.5 percentile of statin adherence, mean refill counts per year were 6.6 and 2.5, respectively. For patients treated by physicians in the top 2.5 percentile and bottom 2.5 percentile of statin adherence, mean refill counts per year were 6.1 and 2.9, respectively.

**Discussion**

The study used a cross-classified hierarchical model to analyze patient adherence to statin therapy. This model estimated the relative variation in patient adherence by physician and pharmacy (random effects) after adjusting for patient, index prescription, and health care provider characteristics (fixed effects). This model was used to avoid key weaknesses of conventional (nonhierarchical) regression models, which neglect clustering of patients within pharmacies and physicians. To our knowledge, this study is the first attempt to assess the degree of variation in adherence that can be attributed separately to physicians and pharmacies, after adjusting for patient case mix.

We found that the percentage of patients on statin therapy dropped sharply after the index fill, with approximately 18% of all statin initiators not having a second fill after the index prescription. A higher number of refills prescribed and lower copayment amount for the index prescription were associated with better adherence to statin therapy. The latter result is consistent with conclusions of recently published studies that analyzed the effects of prescription drug copayments on statin adherence.\(^{32,33}\) A higher number of comorbid conditions, particularly those treated with cardiovascular drugs, was associated with a higher rate of refills, similar to the findings of other studies.\(^{32,33}\)

Our study also found high variation in adherence to statins across pharmacies and physicians that was not explained by patient case mix. The variation in adherence was larger among pharmacies than among physicians.
We observed that patients who filled their statin prescriptions at pharmacies with a high volume of statin prescriptions showed, on average, better adherence. We could not determine whether this observation was because of well-trained pharmacists in the area of cardiovascular disease at these pharmacies, disease management programs, or other factors unmeasured by our analysis.

We also found that, on average, patients treated by physicians who prescribed more statin prescriptions had a lower adherence rate than did those treated by physicians who prescribed fewer statin prescriptions. We did not capture the medical specialty of the physicians in this study and therefore cannot speculate on the possible influence of medical specialty. However, high prescribers may have less time per patient to engage in counseling that may influence adherence to statin therapy. Previous research has shown that general practitioners have more patients using lipid-lowering medications than do specialists, and general practitioners initiate about 80% of prescriptions for statins. All physicians report time pressures, and primary care physicians may have less time per patient.

### TABLE 2

#### Parameter Estimates of Multivariate Cross-Classified Regression Model of Patient Adherence to Statin Therapy

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Parameter Estimate (SE)</th>
<th>Exponentiated Coefficient (exp(β))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>1.446 (0.058)*</td>
<td></td>
</tr>
<tr>
<td>Fixed Effects (β)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤50</td>
<td>-0.146 (0.034)*</td>
<td>0.864</td>
</tr>
<tr>
<td>51-60</td>
<td>0.026 (0.031)</td>
<td>1.026</td>
</tr>
<tr>
<td>61-70</td>
<td>0.034 (0.032)</td>
<td>1.035</td>
</tr>
<tr>
<td>&gt;70</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>-0.045 (0.022)*</td>
<td>0.956</td>
</tr>
<tr>
<td>Region of residence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Northeast</td>
<td>0.016 (0.198)</td>
<td>1.016</td>
</tr>
<tr>
<td>Midwest</td>
<td>-0.040 (0.035)</td>
<td>0.961</td>
</tr>
<tr>
<td>South</td>
<td>-0.215 (0.040)*</td>
<td>0.806</td>
</tr>
<tr>
<td>West</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Pharmacy chain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>0.083 (0.049)</td>
<td>1.086</td>
</tr>
<tr>
<td>B</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>No. of prescriptions dispensed for comorbid conditions</td>
<td>0.020 (0.007)*</td>
<td>1.020</td>
</tr>
<tr>
<td>History of cardiovascular drug use</td>
<td>0.132 (0.026)*</td>
<td>1.141</td>
</tr>
<tr>
<td>Index dose of statin drug</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High dose</td>
<td>-0.088 (0.023)*</td>
<td>0.916</td>
</tr>
<tr>
<td>Low dose</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>No. of index refills prescribed</td>
<td>0.021 (0.003)*</td>
<td>1.021</td>
</tr>
<tr>
<td>Index prescription copayment§</td>
<td>-0.023 (0.004)*</td>
<td>0.978</td>
</tr>
<tr>
<td>Volume of statin patients per physician</td>
<td></td>
<td>-0.067 (0.020)*</td>
</tr>
<tr>
<td>Volume of statin patients per pharmacy¶</td>
<td>0.025 (0.005)*</td>
<td>1.284</td>
</tr>
<tr>
<td>Random Effects</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physicians, $\sigma^2_{u_1}$</td>
<td>0.021 (0.007)*</td>
<td></td>
</tr>
<tr>
<td>Pharmacies, $\sigma^2_{u_2}$</td>
<td>0.035 (0.007)*</td>
<td></td>
</tr>
</tbody>
</table>

* P value <0.001; † P value <0.05; ‡ P value <0.01; § The parameter estimate is calculated based on a $10 increment; ¶ The parameter estimate is calculated based on a 10-patient increment; ‡‡ The parameter estimate is calculated based on an 100-patient increment.
We focused on pharmacy and physician factors in this study, but patient characteristics have been associated with adherence to lipid-modifying therapy. We know from previous research that patients at higher risk for coronary artery disease are more likely to adhere to their treatment than are patients who take it for primary prevention.37

The factors that affect clinical outcomes in lipid-modifying therapy include educating patients, monitoring their response to therapy, and having interventions targeted at behaviors of patients and prescribers.38 In addition, one of the major barriers to adherence is poor communication between the physician and the patient. According to Mariniker et al., patients and physicians should form a therapeutic alliance to “optimize health gain from the best use of medicines, compatible with what the patient desires and is capable of achieving.”39 This is referred to as concordance. To facilitate full concordance, special training in communication may be necessary for health care providers.39

Another opportunity for the health care provider is to identify patients with high risk for nonadherence and to be more aggressive in efforts to monitor and communicate with their patients on an individual basis. Reminding physicians about communicating with their patients regarding the importance of adherence to therapy and providing physicians with a list of their nonadherent patients can positively affect patient adherence from the perspective of population disease management.41

Improving patient adherence may be achieved through pharmacy-based programs, where a combination of patient education and provider awareness is available.42 Since medications are important in the treatment of chronic conditions and because pharmacists have significant knowledge of medications, they play a critical role in disease management.42,43 Pharmacists are the most accessible health care providers to the patient once medication therapy is initiated.38 Therefore, pharmacy care models can promote behavioral changes among patients and should be an important and integral part of the overall treatment plan.

The Asheville Project assessed the clinical, humanistic, and economic outcomes of a community-based medication therapy management (MTM) program. The study found that patients with asthma or diabetes who received ongoing education and long-term MTM achieved and maintained improvements in their condition and had significantly lower disease-related costs.43,44

Assessing adherence by pharmacy characteristics may be of value when it comes to improving adherence with prescribed therapy, particularly for health plans with a commitment to health maintenance. Hierarchical models, such as those employed in this study, can be used to assess unusual performance of specific physicians or pharmacies that represent patients with particularly poor adherence. These providers can be targeted by customized interventions to improve adherence. Of course, in actual practice, statistical analysis can provide only a preliminary indication of suboptimal performance, and more detailed investigation is necessary to verify targets of opportunity for clinical practice improvement.

Limitations
This study relied on the dispensing records of 2 pharmacy chains. While this method in some ways permits more detailed examination of individual patients within a pharmacy chain, it also means that, in our analysis, a patient is lost to follow-up when he or she obtains a refill or new prescription at a pharmacy in a different chain. So the first limitation is that patients who switched pharmacy chains were considered discontinued in our analysis.

Second, exclusion of the only generic statin (lovastatin) creates a limitation of this study, particularly with respect to the relationship between copayment amount and adherence. Our study design, which required a 6-month preindex wash-out period without statin use, resulted in low counts of new generic lovastatin users. Since generic lovastatin has significantly lower cost than the brand statins, exclusion of this drug could potentially have some additional effect on the established relationship between adherence and copayment. However, more than 36% of all patients in our sample paid less than a $10 copayment for the index script. This number is big enough to reliably assess the influence of low copayments on patient adherence.

Third, our analysis included only statin patients with index prescriptions for a 30-day supply, which resulted in the loss of about 23% of the initial patient population. This selection was made to make interpretation of the results more consistent; however, it limits the degree to which our results can be generalized to all statin patients.

Fourth, while pharmacy data are very accurate in recording actual dispensing and prescription pick-up by patients, these data lack information on whether a particular patient actually consumes the medication. However, studies have shown that dispensing data are a good marker for actual use.21 Assuming some nonuse of dispensed drugs, we realize that the reported adherence rates in the present study overestimate actual adherence.

Fifth, although the 2 selected pharmacy chains are nationwide and reasonably representative of the population of pharmacies, patient and pharmacy characteristics within these chains may not be representative.

Sixth, even though this analysis is adjusted for patient and health care provider characteristics, it is likely that not all characteristics that are relevant predictors of adherence were captured. For example, unmeasured patient factors such as severity of disease, patient race, English proficiency, patient income, and educational attainment may be clustered in pharmacies or physician practices and therefore may cause some residual confounding in our analysis. At the health care provider level, we didn’t have information on physician gender, age, years in practice, degree, medical specialty and board training, physi-
Analyses of Attitudes on the Importance of Counseling, the number of staff in physician offices and in pharmacies, and whether some pharmacies operated medication adherence programs.

Seventh, the present model assumes that patients are associated with a single physician or pharmacy, which may not accurately reflect real-life situations. Instead, patients can be treated by several physicians, or they can fill prescriptions at several pharmacies. Such further complexity can be taken into account by the use of so-called multiple membership models, which are very often computationally intractable. However, statin patients using more than 1 physician or pharmacy constituted less than 16% of our original statin patient population (Figure 2), which, along with the large patient sample size and a large number of health care providers in this analysis, should make our results sufficiently robust.

**Conclusions**

Lack of adherence with prescribed therapy is a well-documented problem that can greatly affect patients’ health outcomes. Although the current literature recognizes this problem as multifaceted, it mostly covers the role of the patients and their behavior in adhering to therapy. Our study not only examined the impact of patient characteristics on medication adherence but also examined the possible influence of the pharmacy and the physician in this critical aspect of the treatment.

Our hierarchical modeling approach revealed that there are large variations in patient adherence to statin therapy among both pharmacies and physicians, which translates into a large difference in the refill rates between the best- and worst-performing health care providers at the extreme ends of the distributions. It also showed that high-volume physician practices that prescribed more statins were associated with lower patient adherence. In contrast, pharmacies that dispensed more statins were associated with greater patient adherence to statin therapy.

**Disclosures**

No outside funding supported this research. Authors Alexander Pedan and Laleh T. Varasteh disclose that they have been funded by the internal resources of Adheris, Inc, a vendor of communication materials and interventions designed to increase patient adherence to drug therapy. Author Sebastian Schneeveis is principal investigator of the Brigham and Women’s Hospital DecIDE Research Center, funded by the Agency for Healthcare Research and Quality. He is also funded by grants from the Agency for Healthcare Research and Quality and the National Institute on Aging.

Pedan served as principal author of the study. Study concept and design were contributed primarily by Pedan, with input from the coauthors. Data collection was the work of Pedan, with input from Varasteh; data interpretation was the work of Pedan and Varasteh. Writing of the manuscript and its revision were the work of Pedan and Varasteh.

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Implications of Pharmacogenomics in the Current and Future Treatment of Asthma

Thomas J. Morrow, MD

ABSTRACT

BACKGROUND: For more than a generation, managed care has attempted to eliminate variation in care delivery in the hope of producing predictable outcomes. But the population-based, guideline-driven approach may not have fully appreciated the importance of individual behavior (adherence) and environment, as well as individual genetic makeup. Genetic variation in response to currently recommended therapies may require tailoring medication regimens to the individual patient to achieve optimal outcomes.

OBJECTIVE: To review the pharmacogenomics of asthma and how they impact the medications utilized for its treatment.

METHODS: A search of PubMed that included the time period from January 1991 through September 2005 and the key terms: asthma pharmacogenetics, asthma genetics, asthma response variability, asthma glucocorticoid resistance, asthma steroid-unresponsive, asthma control, beta-agonist genomics, beta 2-receptor abnormalities, asthma genotypes, and leukotriene inhibitor polymorphisms produced 105 articles. Forty-five were rejected for this subject review by failing the following criteria: (1) results in humans, not animals, (2) provide information about clinical implications as well as description of molecular and cellular mechanism of action or the site of action on the gene, and (3) preference for manuscripts that quantified information/results over those that just stated that there were observed differences. The remaining 60 references were reviewed, and 7 references were added after peer review.

RESULTS: There are now limited examples of gene polymorphisms that can influence responses to beta 2-agonists, glucocorticosteroids, and leukotriene modifiers in patients with asthma. Gene mutations that are known to alter the response to asthma therapy include Arg/Arg at position 16, mutations of LTC4S, ALOX5, and GR/NR3C1, increased expression of GR, CRHR1 variants, and mutations in CYP1A2 (-22964 [G/A]), and T 314 allele for histamine N-methyltransferase. Some of these effects associated with these mutations are increased/decreased response to therapy, glucocorticoid resistance, decreased theophylline clearance and possible toxicity, and increased bronchoconstriction.

CONCLUSIONS: Understanding the impact of genetic variations on response to therapy may ultimately improve treatment outcomes for patients with asthma. However, despite substantial progress, no individual gene polymorphisms have been associated with altered responses to asthma treatment in large numbers of patients. It is not yet possible to tailor medication therapy for asthma based on genetic characteristics of individual patients.

KEYWORDS: Asthma, Genetics, Polymorphisms, Treatment response, Outcomes

C

Clinical practice has evolved from anecdotal case reports, to collections of signs and symptoms, to evidence-based medicine. This approach has generally embraced population-based approaches to care to produce a more consistent outcome from different providers. Treatment of both acute and chronic disease is now driven by guidelines based on results from large-scale, well-controlled clinical trials. Examples of well-known guidelines include those for treatment of hypertension, dyslipidemia, diabetes, and depression. In general, treatment guidelines centralize information about phenotypic characteristics (e.g., sex, age, and body weight), patient and family history, and disease severity (e.g., blood pressure and cholesterol level) to drive treatment decisions in a standardized manner. This has led to a dramatic improvement in overall care as it has diminished the variability of individual practitioners in their application of evidence.

The sequencing of the human genome was a fundamentally important step in the evolution of medicine and a quantum leap in our understanding of genes, their association with specific diseases, and new targets of pharmacotherapy. Since the completion of the draft of the human genome in early 2001, gene-based therapies have begun to influence patient care. Advances in the management of hepatitis C, schizophrenia, leukemia, prostate cancer, lung cancer, and breast cancer have all resulted from increased understanding of the genes associated with these diseases. Understanding the manner in which a given patient’s genetic inheritance may influence response to therapy has increased attention on individualization of therapy based on such information.

The highly complex respiratory system is an important pathway for the entry of disease-causing vectors, including viruses, bacteria, fungi, toxins, and antigens. Interpatient
variability in response to treatments for respiratory diseases, such as asthma, is very high, but efforts to understand potential genetic sources of this variability have lagged behind those for other conditions. The objective of this review is to highlight the pharmacogenomics of asthma and how they impact the medications utilized to treat this disease.

### Overview of Asthma

#### Pathophysiology

Asthma is a chronic inflammatory disease of the airways that is characterized by intermittent and at least partially reversible bronchoconstriction, as well as by airway hyper-responsiveness to a wide variety of stimuli. The inflammatory features characteristic of asthma include infiltration of the airways by inflammatory cells that release various cytokines and inflammatory mediators. These mediators result in an increase in airway edema and mucus secretion, hypertrophy, and hyperplasia of airway smooth muscle, and increased airway vascularity, all of which contribute to airflow obstruction. There is wide variability in the pathophysiologic features apparent in different patients with asthma. In many patients, eosinophils are the predominant inflammatory cell type, while in others, neutrophils rather than eosinophils have been shown to be present as the dominant inflammatory cell. Variability in response to medications is also commonly seen in asthmatics. There are many potential reasons for this variability. As noted above, asthma is typically characterized by eosinophil activation and infiltration of the airways, but some patients have increased neutrophils and lack eosinophils in their airways. Such patients may have decreased responses to leukotriene response modifiers and/or inhaled corticosteroids.

#### Epidemiology

Asthma is a very common disease associated with high morbidity. Review of worldwide data indicates that the prevalence of asthma has increased substantially over the last 20 years, but the reasons for this are not clear. Results from the United States indicate that the prevalence of asthma had increased by 75% from 1980 to 1994 and asthma now affects 8% to 10% of the U.S. population. In a survey of more than 42,000 U.S. households, 30% of patients with mild to moderate disease and 70% of those with moderate to severe disease, based on symptoms, reported some level of functional impairment. In 1998, the direct and indirect costs associated with medical care of patients with asthma exceeded $11 billion ($7.5 billion and $3.8 billion, respectively).

### Asthma Diagnosis, Therapy, and Current Treatment Guidelines

#### Diagnosis

Accurate diagnosis is the critical component in the management of asthma. Generally, asthma presents episodic symptoms of airflow obstruction that are at least partially reversible and not attributable to other pathologies. Chronic obstructive pulmonary disease, vocal cord dysfunction in adults, and cystic fibrosis and aspiration in children, must be ruled out in the differential diagnosis of asthma. Spirometric studies utilizing prebronchodilator and postbronchodilator therapy measuring forced expiratory volume in 1 second (FEV1) and peak flow are valuable in measuring reversibility and classifying disease severity. Allergens and irritants that can trigger symptoms or exacerbations should be identified and removed or exposure limited. Thus, while certain features are considered characteristic of asthma, heterogeneity exists in terms of pathologic presentation and response to therapy. It seems logical that genetic variability may explain some of this heterogeneity.

#### Pharmacotherapy

The goal of pharmacotherapy is to successfully maintain normal activity levels, including exercise; control chronic and nocturnal symptoms; optimize pulmonary function; prevent acute episodes of asthma; and avoid adverse effects of asthma medications. Medications used to treat asthma can be divided into 2 general groups: acute-relief medications (i.e., short-acting beta-agonists, and systemic glucocorticosteroids) and chronic-use medications (inhaled corticosteroids, cromolyn/nedocromil, leukotriene modifiers, long-acting beta-agonists, methylxanthines, and omalizumab).

#### Current Treatment Guidelines and Treatment Efficacy

The National Asthma Education and Prevention Program guidelines recommend a stepwise approach to pharmacologic therapy, whereby the amount and frequency of medications are dictated by the severity of the asthma and directed toward suppression of increasing airway inflammation. According to these guidelines, therapy is initiated aggressively to establish prompt control and then slowly stepped-down to minimize the risk of adverse events without sacrificing efficacy. Achievement of treatment goals are less than optimal in many patients. For some this may be due to poor adherence to treatment guidelines, but for a small subgroup, this may be due, in part, to genetic polymorphisms as well as the fact that disease severity may be misclassified in some patients with asthma, resulting in inappropriate therapy. Even treatment that is fully consistent with current guidelines fails to control asthma in some patients. Results of a randomized, stratified, double-blind, parallel-group study of 3,421 patients with uncontrolled asthma showed that fully optimized, long-term drug therapy with inhaled corticosteroids or inhaled corticosteroids plus a long-acting beta-agonist controlled approximately 75% of this group. While these results suggest that the majority of patients could reach guideline-defined measures of control, approximately 25% of these managed patients could not achieve control as defined by the Global Initiative for Asthma and the National Institutes of Health. These results suggest that other factors,
Implications of Pharmacogenomics in the Current and Future Treatment of Asthma

such as severity of disease, concurrent illness, environmental exposures, medication noncompliance, and interpatient genetic variability in response to asthma therapy may play important roles in treatment efficacy. It is reasonable to suggest that current treatment guidelines for asthma therapy should be reviewed in light of the latest information about genetic determinants of responsivity to commonly used asthma therapies.

Genetic Determinants of Responsivity to Asthma Therapy

Genetic factors, including polymorphism in a gene or a random DNA position (single nucleotide polymorphism [SNP]), or in a series of associated alleles, play a role in determining heterogeneous responses to pharmacological treatment among patients with asthma. Drug therapy tailored to an asthmatic patient’s genotype may result in a clinically important increase in efficacy and a reduction in adverse events.

Specific Genetic Mutations That Alter Responses to Different Asthma Therapies

Gene mutations that alter responses to asthma therapy are summarized in Table 1 and described in detail in the following sections.

Beta 2-Agonists

Beta 2-agonists are important bronchodilator drugs commonly used in the treatment of asthma. The beta 2-adrenoceptor gene is expressed in bronchial smooth muscle cells and induces dilation in response to endogenous catecholamine or exogenous triggers. Several polymorphisms have been described in this gene, which is located on the chromosome 5q31-32. Three coding polymorphisms, located at positions 16, 27, and 164, have been studied.

Clinical studies have indicated that the Arg/Arg genotype for residue 16 of the beta 2-receptor alters responses to treatment and disease severity in patients with asthma. Results from one study showed that albuterol-evoked FEV1 was higher and the response was more rapid in Arg16 homozygotes compared with carriers of the Gly16 variant (18% increase versus 4.9% increase, *P* <0.03). Similarly, spirometric assessment of 269 participants in a longitudinal study of asthma indicated that homozygotes for Arg16 were 5.3 times more likely than Gly16 homozygotes to respond (>15.3% increase in FEV1) to challenge with 180 mcg albuterol.

In contrast, clinical trial results have indicated a decreased response to longer-term beta 2-agonist treatment among patients with Arg/Arg genotype for residue 16 of the beta 2-receptor as well as increased risk of exacerbations among patients with this genotype who were treated with a short-acting beta 2-agonist.

The Beta-Adrenergic Response by Genotype trial was designed to establish a genotype-dependent effect of albuterol use on airway function. Patients with mild asthma were enrolled based on clinical criteria and their genotype (Arg/Arg or homozygous for glycine [Gly/Gly]) at the locus encoding the 16th amino acid in the beta 2-adrenergic receptor.

Results showed that patients with the Arg/Arg genotype had increased peak expiratory flow rates (PEFR) when beta 2-agonists were withdrawn as a rescue inhaler and replaced with ipratropium bromide. In contrast, patients with the Gly/Gly genotype showed good responses to beta 2-agonist therapy, that reversed when it was withdrawn. During randomized treatment, patients with the Gly/Gly genotype

<table>
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<th>TABLE 1</th>
<th>Results From Pharmacogenomic Studies That Have Provided Information Relevant to the Treatment of Asthma</th>
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<tr>
<td>Drug Class</td>
<td>Mutation</td>
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<tr>
<td>Beta 2-agonists</td>
<td>Arg/Arg at position 16</td>
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<tr>
<td>Leukotriene response modifier</td>
<td>LTC4S mutation</td>
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<td>ALOX5 mutation</td>
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<tr>
<td>Glucocorticoids</td>
<td>GR/NR3C1 mutations</td>
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<tr>
<td></td>
<td>Increased expression of GR</td>
</tr>
<tr>
<td></td>
<td>CRHR1 variants</td>
</tr>
<tr>
<td>Theophylline</td>
<td>CYPLA2 (-2964 C/G[A])</td>
</tr>
<tr>
<td></td>
<td>T 314 allele for histamine N-methyltransferase</td>
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FEV1=forced expiratory volume in 1 second; GR=glucocorticoid receptor; PEFR=peak expiratory flow rate.
had an increase in morning PEFR of 14 L/min versus placebo with regularly scheduled albuterol. Patients with the Arg/Arg genotype had lower morning PEFR (-10 L/min) during treatment with albuterol than during the placebo period, when albuterol use was limited. The genotype-attributable treatment difference was thus -24 L/min. This information indicates that chronic treatment with a short-acting beta 2-agonist should probably be avoided in asthma patients with the Arg/Arg genotype. It is estimated that 15% (16% of whites and 20% of blacks) of the population is homozygous for Arg16.55,56

A retrospective analysis of relationships between polymorphisms at codons 16 and 27 of the beta 2-adrenoceptor and clinical outcomes in a randomized, placebo-controlled, crossover trial of regularly scheduled salbutamol and salmeterol in 115 patients with mild to moderate asthma indicated that patients with the Arg/Arg genotype had more frequent exacerbations during salbutamol treatment than with placebo (1.91 versus 0.81, P = 0.005).57 No significant treatment-related differences occurred for heterozygous Arg-Gly patients or homozygous Gly-16 patients.58

**Leukotriene Response Modifiers**

Leukotrienes are released from mast cells, eosinophils, and other inflammatory cells in the airways of patients with asthma. Cysteinyl leukotrienes, C4, D4, and E4, released primarily from activated eosinophils and mast cells, are potent contributors to the physiological and pathological changes characteristic of asthma. They are several orders of magnitude more potent than acetylcholine and histamine as contractile agonists of human airways. Leukotrienes increase microvascular permeability, modulate the primary afferent nerve fibers, stimulate mucus release, slow mucus transport, and decrease the activity of human respiratory cilia.

Antileukotriene therapies inhibit synthesis of leukotrienes through 5-lipoxygenase (ALOX5) inhibition or by blocking the cysteinyl leukotriene receptor. The C4 synthesize gene polymorphism (LTC4S) has been correlated with the response of asthma patients to zafirlukast, a leukotriene receptor antagonist. Anderson and colleagues genotyped asthma patients for polymorphisms in the promoter region of ALOX5 and LTC4S. These individuals were participating in a randomized, double-blind, parallel study of inhaled fluticasone (88 mcg twice daily) and zafirlukast (20 mcg twice daily). Results showed that subject's homozygous for mutations in either ALOX5 or LTC4S had a reduced response to zafirlukast. Results from this same study of 68 patients with mild asthma showed that zafirlukast had no activity in LTC4S C/C homozygotes compared with heterozygotes and carriers of the A allele based on percentage change in FEV\(_1\) (-3%, +9%, +9%, respectively). A third study of 23 patients with chronic, severe asthma indicated a different relationship between the LTC4 genotype and response to zafirlukast. In this trial, the FEV\(_1\) response to zafirlukast was increased in heterozygotes and C/C homozygotes while A/A homozygotes had a decrease in FEV\(_1\) with zafirlukast. The reasons for the different patterns of results are not clear, although it may be attributed to differences between population types. Among 114 individuals receiving high-dose zafirlukast, 104 wild-type or heterozygous patients had an 18.8% improvement in FEV\(_1\) after 1 week of treatment. In contrast, 10 patients with the mutant genotype had no benefit from active treatment, as measured by an average change in FEV\(_1\) of -1.2%. None of the patients with the mutant genotype at the ALOX5 core promoter locus manifested a >12% improvement in FEV\(_1\) at the end of the treatment period.

**Glucocorticoids**

Glucocorticoids are the most potent anti-inflammatory drugs used for asthma treatment. They act by binding to an intracellular glucocorticoid receptor (GR) to form a complex. The receptor-ligand complex translocates to the nucleus where it regulates gene expression, decreasing transcription of various proinflammatory proteins and increasing transcription of anti-inflammatory proteins. Glucocorticoids also increase transcription of beta 2-adrenoceptors and muscarinic receptors. This increase in transcription may help to shift airway regulation from vagally mediated bronchoconstriction to sympathetically mediated bronchodilation.

The clinical efficacy of glucocorticoid therapy is derived from a combination of anti-inflammatory effects in the lung, reduction of inflammatory cell survival, and inhibition of inflammatory cytokine production. Despite their well-known efficacy, there is a subset of asthmatic patients who are unresponsive to corticosteroids. These patients demonstrate persistent respiratory symptoms, nocturnal exacerbations, persistent airway obstruction, and inflammation, even though their treatment includes high doses of systemic glucocorticoids. Clinical studies have shown about 5% to 10% of all patients with asthma and up to 35% of those with severe disease have reduced responses to glucocorticosteroid therapy. These patients demonstrate persistent respiratory symptoms, nocturnal exacerbations, persistent airway obstruction, and inflammation, even though their treatment includes high doses of systemic glucocorticoids.

It has been shown that some glucocorticoid-resistant patients have abnormalities in the activity of proinflammatory transcription factors AP-1 and NF-κB. Both AP-1 and NF-κB act by inducing the transcription of chemotactants, cytokines, cytokine receptors, and cell adhesion molecules. Many cases of glucocorticoid resistance may be due to mutations or polymorphisms present in the glucocorticoid receptor gene (GR/NR3C1). A total of 15 missense, 3 nonsense, 3 frameshift, 1 splice site, and 2 alternative spliced mutations have been reported in the NR3C1 gene. These mutations have been associated with glucocorticoid resistance. There are 2 naturally occurring isoforms of the NR3C1: GRα

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**Implications of Pharmacogenomics in the Current and Future Treatment of Asthma**

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(functional) and GRβ (no hormone-binding ability). The glucocorticoid-GRα complex can directly or indirectly alter gene transcription by binding to specific DNA sites or through transcription factor activation. GRα may also be involved with down-regulation of proinflammatory mediators and up-regulation of anti-inflammatory mediators. GRβ is thought to act as an endogenous inhibitor of glucocorticoid action.17-19 Leung and colleagues20 carried out bronchoalveolar lavage (BAL) in 6 steroid-resistant and 6 steroid-sensitive patients with asthma before and after 1 week of treatment with 40 mg/day prednisone. Before prednisone therapy, there were significantly asthma before and after 1 week of treatment with 40 mg/day prednisone. Before prednisone therapy, there were significantly greater numbers of BAL cells expressing IL (interleukin)-2 mRNA (P<0.01) and IL-4 mRNA (P<0.05) in steroid-resistant patients with asthma, as compared with steroid-sensitive patients. There were no between-group differences observed in the numbers of BAL cells expressing interferon (IFN)-γ or IL-5 mRNA expression. After 1 week of prednisone treatment, IL-2 expression was not significantly altered in either group. However, steroid-sensitive patients had a significant decrease in the numbers of BAL cells expressing mRNA for IL-4 (P<0.01) and IL-5 (P<0.001), and a rise in the numbers of IFN-γ mRNA+ cells (P<0.01). In contrast, after prednisone treatment, the patients with steroid resistance had no significant change in either the number of BAL cells expressing mRNA for IL-4 or IL-5.21 An imbalance in the activity of either isoform due to a genetic anomaly may increase the risk of glucocorticoid resistance. The synthesis of glucocorticoid receptors is strongly influenced by interleukins. Genetic polymorphisms that alter expression of several interleukins have been associated with reduced responsivity to corticosteroids in patients with asthma.22-24 To date, 2 types of steroid-resistant (SR) asthma have been identified: type I (>95% of cases) is cytokine induced and is associated with increased expression of GRβ, a less active GR isoform, and type II (<5% of cases) is due to low numbers of GRs. Clinically, Type I SR asthmatic patients present with severe side effects, including adrenal gland suppression and Cushingoid features. Type II SR asthmatics have a generalized primary cortisol resistance and do not develop steroid-induced side effects.49

Other genetic factors may impact response to corticosteroid therapy. CRHR1 is the primary receptor mediating the release of adrenocorticotropic hormone, which regulates endogenous cortisol levels and genetic variation in CRHR1 that is associated with improved pulmonary function response to inhaled corticosteroids.50 The mean percentage change in FEV₁ for those homozygous for the minor allele was 13.3% versus 5.5% for those homozygous for the wild-type allele.49

Other Therapies
Genetic factors may also influence the safety and efficacy of other commonly used asthma treatments. Cytochrome p450 (CYP) 1A2 is involved in the metabolism of theophylline, and a polymorphism for the gene encoding this enzyme, -2964 (G/A), has been correlated with reduced theophylline clearance versus that in patients with the G/G genotype. Thus, theophylline may require reduced dosing in patients with the A allele at site -2964 (G/A) in the CYP1A2 gene to avoid possible toxicity.51

Histamine is a bronchoconstrictor involved in the pathogenesis of asthma, and histamine N-methyltransferase plays a central role in histamine catabolism in bronchial tissue. The T 314 allele of the gene for histamine N-methyltransferase results in decreased enzyme activity and possibly also increased bronchoconstriction in patients with asthma. It may be important to use antihistamines that do not, themselves, inhibit this enzyme in asthma patients with the T 314 allele.52 Eotaxin (chemokine, CC motif, ligand; CCL11) is a potent eosinophil chemoattractant that plays a significant role in the pathology of asthma. Recent results have indicated that the genetic variation at the CCL11 locus is an important determinant of serum total IgE levels among patients with asthma,53 and it is reasonable to suggest that CCL11 genotype may influence the response to medications that exert their effect via IgE receptors. Omalizumab is a recombinant anti-IgE antibody therapy for asthma targeted at patients with elevated IgE levels.54 Thus, in theory, this genotype might predict a positive response to omalizumab in asthma patients, but studies carried out, to date, have not evaluated this possibility.

The results presented in this section indicate that there are numerous genetically influenced pathways that contribute to the wide interpatient variability in response to commonly prescribed asthma therapies. Currently, national guidelines do not suggest testing for these variations. These and other undiscovered variations will undoubtedly play a significant role in the future of defining the proper therapy for each individual. Additional research is required to more accurately predict therapeutic responses based on individual patient genotypes.

### Integration of Molecular Diagnostics With Therapeutics

#### Economic Considerations for Pharmacogenomics

Economic considerations need to be considered in the application of pharmacogenomics to clinical therapy. A set of cost-effectiveness criteria has been proposed to determine when pharmacogenomics is appropriate in selection of therapy and can act as a guide for future research. These criteria include: (1) disease has a severe outcome, defined as a significant impact on the quality of life, or has expensive medical care costs, or has a high mortality; (2) a drug’s response is currently not monitored or there is difficulty in monitoring the response; (3) there is a strong association between gene variant and clinically relevant outcomes; (4) a rapid and relatively inexpensive assay is available; and (5) variant allele frequency is relatively high (Table 2).55 These criteria could eventually be considered in the drug selection processes utilized by managed health care plans. The majority of managed health care plans use prior-
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<table>
<thead>
<tr>
<th>TABLE 2</th>
<th>Framework for Evaluating the Potential Cost-Effectiveness of Pharmacogenomic-Based Therapies</th>
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<tr>
<td><strong>Factors</strong></td>
<td><strong>Characteristics Favoring Cost-Effectiveness</strong></td>
</tr>
<tr>
<td>Severity of outcome avoided</td>
<td>Severe outcomes, which include high mortality, significant impact on quality of life, or expensive health care costs</td>
</tr>
<tr>
<td>Drug monitoring</td>
<td>Drug-response monitoring that is currently not practiced or difficult</td>
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<tr>
<td>Genotype-phenotype association</td>
<td>Strong association between gene variant and clinically relevant outcomes</td>
</tr>
<tr>
<td>Assay</td>
<td>Availability of a rapid and relatively inexpensive assay</td>
</tr>
<tr>
<td>Polymorphism</td>
<td>Relatively high frequency of variant allele</td>
</tr>
</tbody>
</table>

An early yet growing body of evidence shows that incorporating our understanding of genomics into clinical practice can lead to clinical benefit. Genetic predictors of responses to specific therapies could be helpful in patients with asthma and clinicians should be educated regarding these determinants.63,64

At present, there has been little integration of genomics and genetic testing for determination of best approaches to therapy for patients with asthma. However, results from several studies might have “set the stage” for this approach. For example, it has been noted that the association of the CRHR1 gene, as well as 1 specific haplotype within the CRHR1 gene, with the degree of response to inhaled corticosteroids, may provide the basis for a first step in the development of individualized therapy for asthma.65

However, the applicability of genomic and genetic testing faces significant challenges. Patients are likely to be uncomfortable without the presence of confidentiality safeguards. Physicians will be faced with a bewildering array of testing from competing vendors. Managed care companies will face difficulties in tracking and managing the utilization of these complicated tests due to potentially high costs and lack of an adequate coding system for billing. They will also face difficulties in coordinating all of the contracts in a rapidly expanding field. Pharmaceutical companies will face situations in which decisions to control utilization of their products are influenced by testing that is likely to be less than 100% sensitive or 100% specific. Patients will be caught in the middle.

It is obvious that standards of care will be sorely needed to guide this process. Most importantly, it is essential that future clinical trials demonstrate that the clinical benefits achieved with therapy selected on the basis of pharmacogenetic analysis justify the cost of testing. A recent modeling study carried out by Stallings and colleagues compared the annualized per-patient cost testing all asthma patients for nonresponse genotype prior to treatment versus no testing. They estimated that the savings associated with the testing strategy ranged from $200 to $767.
per patient and concluded that testing costs would be more than offset by avoided nonresponse costs.66

Conclusions

We now have more information about the genetic underpinnings of interpatient variability in response to therapies used in patients with asthma. There are clear examples of gene polymorphisms that can influence responses to beta 2-agonists, glucocorticosteroids, and leukotriene modifiers. However, it must be remembered that despite substantial progress, no individual gene polymorphisms have been associated with altered responses to treatment in large numbers of patients, which is critical to obtain prior to fielding gene testing.67

Emerging results for a wide range of diseases, including asthma, indicate that standards of care established in treatment guidelines may not be uniformly applicable to the entire population of patients with a given disease because of multiple causes, one of which is gaining recognition: genetic variation in treatment response. In asthma, there is significant genetically determined variation in response to the 3 main modes of therapy: inhaled corticosteroids, beta 2-agonists, and leukotriene response modifiers. These genetically determined variations in response are important to keep in mind when clinicians make modifications to therapeutic regimens for asthma therapy to achieve control of symptoms and exacerbations. Understanding the impact of genetic variations on response to therapy has the potential to improve care, decrease side effects, and improve patient outcomes.

Managed care physicians and patients will soon enter a new era of complexity that will require significant education. It is important that they understand the therapeutic as well as the social and economic implications of our increased understanding of both the genetics of disease and responses to specific therapies. There are important and difficult ethical issues related to genetic testing (e.g., cost insurability, employability, medical prognosis and treatment decisions based on genetic information) that must be addressed by both health care providers and society in general.

DISCLOSURES

No outside funding supported this research. Author Thomas J. Morrow worked as an independent consultant and had a primary affiliation with Teva Neuroscience during the time that this article was prepared. After submission of this article, the author joined Genentech as a director in the Value-Based Health department.

REFERENCES


Implications of Pharmacogenomics in the Current and Future Treatment of Asthma


ABSTRACT

BACKGROUND: Prescription assistance programs (PAPs) are offered by pharmaceutical manufacturers to provide medications at no out-of-pocket cost to various categories of medically indigent patients. Some PAPs require only 1 application whereas others require as many as 4 applications per year per drug per patient, depending on the manufacturer’s requirements. OBJECTIVE: To measure the costs incurred by a medical clinic that provides chronic prescription medications via PAPs. METHODS: This project was conducted in a free-standing, inner-city, Midwestern health clinic on the PAP application process for 1 representative drug for 32 pharmaceutical manufacturers that offered PAPs for drugs taken on a long-term basis for chronic conditions. Time and motion studies were conducted using a medical assistant with the greatest amount of PAP experience. Assessment of time-to-access and time-to-complete forms was performed outside of normal clinic business hours to avoid interruptions. Personnel time costs also included receipt and delivery of drug to the patient (drug distribution time), which were assessed during normal business hours for actual medications received for 10 patients and included the time required to notify the patient of the arrival of the drug and to dispense the medication to the patient. Supply costs for this PAP service included printing and copying costs. Submission costs associated with mailing or faxing the documents were determined and calculated using the price of materials only. Total application cost was calculated by adding the personnel time cost, supply cost, and submission cost. Annual PAP time was the time spent completing PAPs for 1 medication for 1 patient for 1 year. The time and resources required and the associated costs were aggregated separately for the pharmaceutical manufacturers that required 1, 2, or 4 applications per drug per patient per year. RESULTS: The total average application cost for all 32 companies was $25.18 (SD, $17.23). Personnel time costs accounted for half or more of the total application cost, regardless of submission mode. The time to complete the form for any PAP was 0:06:20 (SD, 0:05:03) minutes with a range from 0:03:01 to 0:34:22 minutes. Printing costs were $0.20 (SD, $0.10) and copying costs were $1.96 (SD, $0.21). Average supply costs were $2.16 (SD, $0.23). Faxing versus mailing PAPs saved $17.90 per application. Total annual clinic cost to assist patients in obtaining drugs through a PAP ranged from $10.42 per patient for a drug that requires 1 application per year (15 manufacturers, 47%) up to $46.30 per patient for a drug in a PAP that requires 4 (re)applications per year (12 of 32 manufacturers, 38%).

CONCLUSION: The number of PAP applications required per patient per medication annually has the greatest impact on clinic time and financial resources. Application submission method also influences the overall costs of providing this service in the clinical setting. Medical clinics should base their decision to provide a PAP application service to patients on the time and costs associated over the course of 1 year and not on the 1-time application cost.

KEYWORDS: Pharmaceutical assistance program, Medically indigent, Costs; Primary care

J Manag Care Pharm. 2007;13(6):506-14
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What Is already known about this subject

- There is little information in the literature about the cost to physician offices that is incurred by providing prescription assistance programs (PAPs) to their patients.

What this study adds

- Total annual clinic cost to assist patients in obtaining drugs through a PAP ranges from $10.42 per patient for a drug that requires 1 application per year (15 of 32 manufacturers, 47%) up to $46.30 per patient for a drug in a PAP that requires 4 (re)applications per year (12 of 32 manufacturers, 38%).

Change is required so that alternative methods of providing and financing health care will extend coverage to low-income groups with high health care needs.3,4 Despite this proclamation, written 20 years ago by Dr. H.P. Eken, the inability of the low-income or medically indigent population to pay for prescription drugs in the United States continues to be a barrier to receiving them. According to the Centers for Medicare & Medicaid Services, spending on prescription drugs increased 5.8% in 2005.2 As health care costs increase, and in particular, prescription drug costs, the disparities between the manufacturers’ prices and the consumers’ ability to pay for treatment will widen.

Medically indigent patients often do not meet requirements for Medicaid eligibility but are unable to afford private insurance coverage. In 2005, a family of 4 with an annual household income at or below $19,350 was considered to be living below the poverty level.3,4 However, $14,512 (75% of federal poverty level) was the cutoff for Medicaid eligibility.3,4 It is likely that this household could not afford private health insurance with prescription drug coverage, and it would fall into this medically indigent category.
Knowing the status of health care coverage for patients is vital for providers to better serve their patients’ medical needs. The benefits of providing prescription drugs to medically indigent patients who are otherwise unable to pay for them are well documented. By complying with proper treatment regimens, patients are less likely to develop secondary disease associated with improper pharmaceutical compliance.

Pharmaceutical company prescription assistance programs (PAPs) are designed to provide access to medications for those who are uninsured and unable to pay for their medications. Strum and colleagues found that offering the manufacturer PAP service to their patients with diabetes reduced low-density lipoprotein cholesterol and hemoglobin A1C values significantly. Additionally, patients could have access to more medications after they were enrolled in PAPs than when they were paying for their prescriptions themselves. Providing free or low-cost prescription drugs helps to improve medication adherence and reduces hospitalization rates as well as emergency room visits.

The inability to pay for prescription drugs causes premature loss of life, loss of potential work time, and decreased quality of life.

Research has shown that health care institutions, in addition to improving patient outcomes, can reduce bad debt claims resulting from uncompensated prescriptions by implementing their own PAPs. The cost of caring for the medically uninsured, indigent population usually falls on the local hospitals that treat these patients as an ambulatory outpatient service. Without access to needed medications, disease often progresses and emergency therapy is often needed to avoid acute complications or death. Therefore, physicians and medical groups that choose to forgo PAP participation because of administrative cost and/or time concerns may ultimately bear financial responsibility for these patients.

In 2004, PAP access expanded to more than 22 million prescriptions, representing as much as $4 billion in medications for patients. Despite these numbers, PAPs are often underused because of the complex application process. In fact, even using the heavily promoted www.pparx.org Web site, individuals are still instructed to go through their doctor’s office to complete the application process: “Here are the assistance programs that you have selected. Some of the applications require that you contact the company, others need to be filled out and signed by your doctor. You can print the applications and details sheets for those programs that don’t have applications available now or you can use our online application wizard to fill out all of the ‘online available’ applications at once. You can then print them and deliver them to your doctor.”

Most medically indigent patients are unable to participate in PAPs without assistance from health care professionals, many of whom lack time, training, or incentive. Some institutions have assigned personnel and established specific protocols to assist patients and providers in completing and submitting the PAP application forms and supporting documentation.

This processing requires several steps, including completing the form in its entirety, providing an original signature by the prescriber, attaching the prescription and any required financial information, submitting this information to the manufacturer, and often requiring receipt of the medication at the prescriber’s office between 2 to 8 weeks following submission of the PAP form. Additionally, the majority of PAPs provide a 3-month supply of medication at one time and require a new application for each subsequent quarterly supply; hence, 4 application submissions per year.

To date, there have been no published data describing personnel time and material costs incurred by organizations providing this service to patients. The objective of this study was to measure the costs incurred by a medical clinic that provides chronic prescription medications via PAPs.

Methods

This project was conducted in a free-standing, inner-city, Midwestern health clinic serving more than 13,000 medically indigent patients with more than 47,500 patient encounters in 2005-2006. The Kansas City Free Health Clinic has extensive experience using PAPs, having processed more than 3,250 PAP applications annually since 2001. A total of 143 unique medications from 39 pharmaceutical companies were initially considered for inclusion. Drug inclusion criteria were both approved by the U.S. Food and Drug Administration for use in a chronic medical condition that requires ongoing use (refills) to appropriately treat the condition and obtainable via a PAP.

In the early stages of data collection, it was determined that each pharmaceutical company had a unique application form but identical PAP requirements for different drugs within each company. On the basis of this finding, 1 representative drug from each company was used to generate project data. PAP forms vary among pharmaceutical manufacturers with respect to (1) qualification standards, (2) submission criteria, and (3) supporting documentation required. Therefore, the unique PAP application requirements from each company were analyzed individually using 1 drug from each manufacturer. Additionally, it is imperative to note that the necessary components to complete the application, the structure and organization of the application, and the number of signatures vary by each manufacturer, making it vital to assess the time necessary to complete each unique manufacturer’s application. The time and resources required and the associated costs were aggregated separately for the pharmaceutical manufacturers that required 1, 2, or 4 applications per drug per patient per year.

Time and motion studies were conducted based on previously published methodologies. Medical assistants were assigned to complete PAP applications because they were (1) capable of completing the forms and (2) determined to have the lowest annual payroll cost per full-time equivalent salary. Only the medical assistant with the greatest amount of PAP experience...
was used for the time and motion study to eliminate the potential confounder of unfamiliarity with the PAPs. The study of time-to-access and time-to-complete forms was performed outside of normal clinic business hours. This method was used to avoid counting time costs associated with interruptions in workflow during a customary business day. Each application was completed 3 times by the experienced medical assistant and recorded by one of the authors (Mangum).

All applications were accessed via 1 of 2 Internet search engines—the Partnership for Prescription Assistance (www.pparx.org) or a nonprofit organization (www.needymeds.com). These 2 search engines were used because of their extensive inventory of PAP forms.

Total application cost was calculated by adding the personnel time cost, supply cost, and submission cost that are outlined and defined in Table 1. Personnel time cost from receipt of drug to delivery to the patient (drug distribution time) was assessed by time and motion observation performed by 1 of the authors (Mangum) of the actual medications received for 10 patients. This time measurement was the only component of personnel cost that was completed during normal clinic hours (drugs are not received on weekends). It is the medical clinic’s policy to have all drugs delivered to the clinic and not directly to the patient because of the variable quality of housing situations among clinic patients and uncertainty regarding home receipt and accountability for the drugs. Once a medication was received, personnel, under the supervision of a physician, record, label, and store the drug at the clinic.

The oversight by the physician is an added safety check and one that is required by the clinic. Because the time from PAP application submission to receipt of medication may be as long as 8 weeks, this verification is designed to ensure no change in medication therapy has occurred since the request was forwarded to the manufacturer. Realizing that the medication is checked for accuracy by the drug manufacturer before shipping and that this added step in our clinic may be unique, we did not include the physician’s time in the analysis. The other components of the drug distribution time portion of total personnel cost include the time required to notify the patient of the arrival of the drugs and the time to dispense the medication to the patient. This part of the PAP process is the same for all medications received and therefore does not differ among the PAPs.

Personnel time cost also included the time to access and complete forms. The information necessary to complete the forms was categorized into 5 general sections: (1) patient information, (2) health care provider information, (3) prescription

<table>
<thead>
<tr>
<th>TABLE 1 Description of Time and Material Costs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cost Category</strong></td>
</tr>
<tr>
<td>Personnel time costs ($0.27 per minute)*</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Supply costs ($)</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Submission costs ($)‡</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Total application cost ($)</td>
</tr>
</tbody>
</table>

* Based on mean hourly wage for medical assistants ($12.21) plus benefits ($4.23), resulting in total hourly cost of $16.24 divided by 60 minutes.
† Based on accepted market values.
‡ Submission costs included only the cost of submitting the document itself and do not include the cost of personnel time involved in the submission of those documents.
§ United States Postal Service (USPS) standard priority mail envelope and base price were used to determine costs. Postage was also calculated using standard priority envelope and flat rate posted on the USPS Web site.

was used for the time and motion study to eliminate the potential confounder of unfamiliarity with the PAPs. The study of time-to-access and time-to-complete forms was performed outside of normal clinic business hours. This method was used to avoid counting time costs associated with interruptions in workflow during a customary business day. Each application was completed 3 times by the experienced medical assistant and recorded by one of the authors (Mangum).

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information, (4) financial and insurance documentation, and (5) other information such as phone calls, advocate enrollment, or credit checks (Table 2).

Supply cost for this PAP service included printing and copying costs. The same computer, printer, copier, fax, and charting system were used for all PAPs to ensure that the mechanical speed of different machines was not a factor in the final results (Table 1).

Submission cost associated with mailing or faxing the documents was determined and calculated using only the price of materials involved in submitting the documentation and did not include personnel time cost (Table 1).

As part of this clinic’s submission process, personnel make 2 copies of the application and all supporting documents. One set of copies is given to the patient for his/her records, while the other set is placed in the patient’s medical record. If the application is mailed, the original application and supporting documents are sent. Alternatively, if the application is faxed, the original documents are destroyed once successful transmission of the fax has occurred. For purposes of this study, the actual documents were not sent to the pharmaceutical company because patient information was fictitious. The times required by the pharmaceutical company to process the application, fill the prescription, and deliver the prescription were outside the scope of this study.

Annual PAP time was the time spent completing PAPs for 1 medication for 1 patient for 1 year. Twelve of the 32 companies (38%) required a new application with each prescription order for 3 months (meaning 4 PAP forms per patient per year per medication), while 5 manufacturer PAPs (16%) required 2 application forms per patient per year, and 15 manufacturers (47%) required only 1 application each year (Table 3).

Time measurements were collected in an hour:minute:second format and depicted as such. Cost components were described in U.S. dollars and cents. Means and standard deviations were tabulated for all components. Differences in time and costs associated with submission methods and the number of applications required per year were analyzed by multivariate analysis of variance, followed by univariate analyses and post hoc testing, as appropriate. This project was approved by the Kansas City University of Medicine and Biosciences and the University of Missouri–Kansas City Institutional Review Boards.

Results

Thirty-nine pharmaceutical companies were originally considered for analysis. Data analysis was conducted on the 32 pharmaceutical companies that met the stated inclusion criteria. Total application cost is displayed in Figure 1. The average total application cost for all 32 companies was $25.18 [SD, $17.23] and ranged from $7.73 (Bristol-Myers Squibb Company) to $58.13 (GlaxoSmithKline PLC). Personnel time cost accounted for half or more of total application cost, regardless of submission mode. The average time required to complete the forms for all PAPs was 0:06:20 [SD, 0:05:03] minutes with a range from 0:03:01 to 0:34:22 minutes. Drug distribution time was 0:06:35 [SD, 0:01:12]. Average printing costs were $0.20 [SD, $0.10] and photocopying costs were $1.96 [SD, $0.21]. Seventy-five percent (n=24) of application packets were 4 pages long and required 10 pages of supporting documents. Collectively, this resulted in average supply costs of $2.16 [SD, $0.23]. The submission cost

<table>
<thead>
<tr>
<th>TABLE 2 Typical Information Required to Complete Prescription Assistance Program Forms</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient information</strong></td>
</tr>
<tr>
<td>1) Name</td>
</tr>
<tr>
<td>2) Address</td>
</tr>
<tr>
<td>3) Phone number</td>
</tr>
<tr>
<td>4) Social Security number</td>
</tr>
<tr>
<td>5) Date of birth</td>
</tr>
<tr>
<td>6) Number in household</td>
</tr>
<tr>
<td>7) Employer information</td>
</tr>
<tr>
<td>8) Income/assets amount</td>
</tr>
<tr>
<td>9) Income source</td>
</tr>
<tr>
<td><strong>Health care provider information</strong></td>
</tr>
<tr>
<td>1) Physician’s name</td>
</tr>
<tr>
<td>2) Medical specialty</td>
</tr>
<tr>
<td>3) State licensure number</td>
</tr>
<tr>
<td>4) DEA number</td>
</tr>
<tr>
<td>5) Medical clinic’s address</td>
</tr>
<tr>
<td>6) Medical clinic’s phone number</td>
</tr>
<tr>
<td>7) Medical clinic’s fax number</td>
</tr>
<tr>
<td>8) Primary clinic contact</td>
</tr>
<tr>
<td><strong>Prescription information</strong></td>
</tr>
<tr>
<td>1) Drug</td>
</tr>
<tr>
<td>2) Daily dosing information</td>
</tr>
<tr>
<td>3) Directions for use</td>
</tr>
<tr>
<td>4) Quantity</td>
</tr>
<tr>
<td>5) Refills/duration of therapy</td>
</tr>
<tr>
<td><strong>Financial and insurance information</strong></td>
</tr>
<tr>
<td>1) Tax forms</td>
</tr>
<tr>
<td>2) Pay stubs</td>
</tr>
<tr>
<td>3) Bank statements</td>
</tr>
<tr>
<td>4) Health insurance qualification</td>
</tr>
<tr>
<td>5) Social Security benefits statements</td>
</tr>
<tr>
<td>6) Medicaid denial letter</td>
</tr>
<tr>
<td>7) Alimony/child support</td>
</tr>
<tr>
<td>8) Unemployment</td>
</tr>
<tr>
<td>9) Veterans benefit</td>
</tr>
<tr>
<td>10) Pension/retirement</td>
</tr>
<tr>
<td><strong>Other information</strong></td>
</tr>
<tr>
<td>1) Phone calls</td>
</tr>
<tr>
<td>2) Advocate information</td>
</tr>
<tr>
<td>3) Patient credit checks</td>
</tr>
</tbody>
</table>

* To decrease variance and with consideration for HIPAA, all forms were completed with the same fictitious patient’s information with the exception of GlaxoSmith-Kline’s “Bridges to Access,” which requires actual patient information to receive a patient advocate number assignment.

† One or more of these documents may be required by the pharmaceutical company. For the purposes of this study, a fictitious patient would answer all questions and have all necessary documentation available at the time of form completion.

DEA=Drug Enforcement Administration; HIPAA=Health Insurance Portability and Accountability Act.
incurred by mailing compared with faxing the application was a higher proportion of the total application cost. Faxing versus mailing PAPs saved $17.90 dollars per application.

The average annual PAP time and costs are displayed in Figure 2. The annual PAP time was directly affected by the number of applications required per year for each medication. As can be seen in Figure 2, the increase in annual PAP time associated with multiple PAP applications for the same drug for the same patient had a directly proportional but not linear effect on annual PAP time and cost. Annual PAP time was also affected by method of submission. Mail submission (n=27) required an average of 0:49:18 [SD, 0:32:18] minutes, approximately 0:25:00 and 0:21:00 minutes more than fax (n = 4, 0:24:13 [SD, 0:11:32] minutes) or Internet submissions (n = 1, 0:28:20 minutes), respectively. Personnel time associated with 4 applications accounted for 48.1% to 52.4% of total annual cost per drug per patient and varied by the submission method (Figure 2).

■ Discussion

Using office personnel to provide medications to patients via PAPs is a costly endeavor. Over 4 years beginning in 2001, our medical clinic spent $327,240, or $81,835 annually, for this service.32 Not surprisingly, PAPs that required more than 1 application per patient per year and had to be mailed were the most costly. Mailed applications had an average total cost of nearly 3 times the cost of applications submitted by fax, $28.03 versus $10.13. PAPs that required 4 applications per drug per patient per year had an annual cost that was more than 4 times the cost ($46.30) of a manufacturer that required 1 application per year ($10.42).

It is important to note that a PAP that requires 4 applications per year does not simply require completing the “once-annual” application and submitting it 4 times. Instead, it involves...
collecting updated information from the patient (Table 2) and repeating the entire process 3 more times. Each PAP requires a different amount of information necessary to complete the application; hence, each manufacturer’s application is unique. One cannot simply take the cost necessary to complete the application for a company that requires only a once-annual submission and multiply it by the number of each reaplication for another company and expect to appropriately judge the cost of time to complete the application. These estimated PAP costs were minimized through the use of lower-payroll personnel, time of observation (e.g., outside of normal clinic hours for some of the observations), and personnel familiarity with the various PAP process and information requirements.

Support for the personnel time and cost findings for this study can be found in the literature. Previous research conducted by Richardson and Basskin in a survey of 118 safety-net providers, of which 52 were in a clinic setting, illustrated that respondents reported that paper applications required an average of 0.4 hours found in the present study. Sarrafizadeh and colleagues estimated the personnel time in a private ambulatory care clinic study, and 0.8 hours per electronic submission, twice the 1.1 hours, 36% more than the average 0.81 hours in the present study, in 1999-2000 that included a PAP service, and drug cost savings were minimized through the use of lower-payroll personnel, time of observation (e.g., outside of normal clinic hours for some of the observations), and personnel familiarity with the various PAP process and information requirements.

Our study directly measured the time necessary for personnel to complete applications, whereas these previous studies used only estimates of personnel time. Another potential for the variance in PAP time requirements across studies may be explained in part by our methods, in that the time and motion studies for completing the applications were conducted outside of normal clinic hours. Weiner and colleagues reported 6-month operation costs of $110,537 for a broad-scope patient assistance program in 1999-2000 that included a PAP service, and drug cost savings of $237,985 that included a PAP cost offset in free goods of $31,028 (13%). This study included overhead, higher-salaried personnel without breakdown by type of personnel, and did not report the volume of PAP applications. This broader-scope patient assistance program to obtain lower-cost medications had an operating cost, if annualized, of $958 per patient, delivering about $2,060 per year in drug cost savings or a savings-to-cost ratio of about 2.2-to-1.

Meaningful comparison of our findings and prior studies were made difficult as a result of methodological differences. Other programs, for instance, charge a fee for each prescription filled in the PAP to offset expenses for the program. More important, before the present study, physicians were unable to use these data to predict the feasibility of providing this service in their own setting because a projected cost per PAP had not been determined. As an example of the value of the present study, it is possible to estimate a projected increase of 206% in personnel costs compared with our results if a registered nurse is used rather than a medical assistant.

It should be noted that all of the companies that participate in PAPs are brand-name drug companies. In community practice, there is often a therapeutically equivalent generic alternative in the same drug class as the prescribed medication. In theory, prescribing the generically available alternative in place of the

![Figure 2](image-url)

**Annual Cost Per Patient Per Prescription Assistance Program by Number of Applications**

- The line represents the annual PAP time.

<table>
<thead>
<tr>
<th>Annual PAP Cost ($)</th>
<th>1 Application (N = 15)</th>
<th>2 Applications (N = 5)</th>
<th>4 Applications (N = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean [SD]</td>
<td>% of Total Cost</td>
<td>Mean [SD]</td>
<td>% of Total Cost</td>
</tr>
<tr>
<td>Personnel time cost (A)</td>
<td>5.04 [0.30]</td>
<td>48.4</td>
<td>10.29 [1.74]</td>
</tr>
<tr>
<td>Supply cost (B)</td>
<td>2.16 [0.00]</td>
<td>20.7</td>
<td>3.62 [1.57]</td>
</tr>
<tr>
<td>Submission cost (C)</td>
<td>3.22 [1.30]</td>
<td>30.9</td>
<td>4.90 [3.87]</td>
</tr>
<tr>
<td>Total application cost</td>
<td>10.42 [1.36]</td>
<td>100.0</td>
<td>18.80 [6.39]</td>
</tr>
</tbody>
</table>

* A multivariate analysis of variance showed a significant effect of application number on time and costs, F(4,56)=61.126, P<0.001, partial eta-squared=0.814. Univariate tests conducted separately on time and cost both showed significant effects, F(2,29)=147.16 and 343.127, partial eta-squared=0.910 and 0.959 for time and cost, respectively, P<0.001. Post hoc tests using Bonferroni’s test each showed that the time and cost of 1, 2, and 4 applications was significantly different from each other.
brand-name drug would lower the overall health care cost for the patient. However, some of these patients who use PAP programs have difficulty even paying for generic drugs, which would lead to noncompliance, disease progression, and/or increased overall health care costs. This is why the prescribing of brand-name drugs and the use of PAPs are essential for the care of some clinic patients.

There are some alternatives to providing PAPs in medical offices. Two Internet sites (www.pparx.org and www.rxassist.org) provide eligibility information and downloadable prescription assistance applications. These sites are efficient to use in locating forms and instructions compared with the alternative method of trying to find PAP information on each individual pharmaceutical Web site. The features of these Web sites improve the initial access to the manufacturer’s application and provide accurate manufacturer contact information but do not eliminate the majority of time and costs that must be assumed by medical offices to provide PAP services for patients.

Outsourcing assistance for patients to obtain drugs through PAPs is another option, since not every medical practice can afford to provide the necessary personnel and materials. As such, others have reported savings of $27,000 per year by using an outside source to assist patients in completing PAPs. Locally, community health centers and the United Way have developed programs to improve access to medicines for the medically indigent. Physicians in communities with these resources available can provide contact information and patient brochures about these services in their offices. In many cases, these organizations already have the established clerical support in place and require minimal charge, if any, to provide application assistance. Internet groups such as The Medicine Program and Medicine Bridge offer patients help in obtaining and completing PAPs, albeit for a fee. More recently, Patient Assistance Program Solution (www.paprx.com) has begun offering a software package to assist with the PAP process. No formal comparison has been conducted, to date, among the various assistance programs.

Recently, another local metropolitan free health clinic incorporated the use of a computerized program to assist with the PAP process. This clinic is staffed completely by volunteers and open only 1 night each week. In 2005, the clinic served more than 350 patients in 26 different zip codes. Since the clinic opened in 2000, more than 6,000 patient visits and more than $1.3 million in free medications have been donated by pharmaceutical PAPs, with more than 1,900 PAP applications processed in 2006. This clinic serves a similar population to the one described in the present study, and it is possible to estimate from our data the time that might be saved by using a computerized program for the PAP process. From our data in Table 2 and assuming that the supply and submission cost would be similar between the 2 clinics because the computer system did not change the submission modalities or the additional forms necessary to process PAPs forms, the time to complete an application is reduced to 0:02:13 minutes compared with more than 0:06:00 minutes with manual writing. This time savings is offset by the upfront personnel time that is required to input all the data for each patient into the computer system and to keep it updated, as well as the cost of the software and annual renewal fees. While all the staff are volunteers in that comparison free health clinic so there is no personnel time cost, this alternative method of completing PAPs may provide additional information to clinics evaluating the feasibility of providing patients with assistance in using PAPs.

“Development of a ‘universal’ PAP application process would greatly benefit patients and health care providers as well as reduce personnel time required to complete individual applications,” according to Chishom and DiPiro. Often the reasoning behind making the process as complex as it is lies in the pharmaceutical companies’ requirement to determine income eligibility and if alternative sources of funding are available to the patient. However, the need to verify eligibility more than once a year seems questionable. Nevertheless, having the forms available to patients in a more universal, standardized format and without requiring prescriber information other than the prescription itself would solve much of the problems and the professional time required.

Requiring the prescriber’s signature on the individual application to verify the information provided on the application and certify that there is no falsification of data seems unnecessarily burdensome. This requires time of the clinic staff and prescriber as well as the patient to have the prescriber give an additional signature if the clinic does not offer a PAP service. This requirement of a second signature by the prescriber on the PAP application makes it impossible for a patient to take the prescription from the prescriber, download the form from a public place, and submit the PAP directly. Rather, the patient must make a second trip to the prescriber for his or her signature to certify that the PAP form submitted by the patient is truthful and complete.

If the application is approved by the pharmaceutical manufacturer and the medication is mailed, the majority of manufacturers mail the medication directly to the prescriber. This requires that someone at the medical clinic accept the mailed prescription and contact the patient. Then the indigent patient must again incur a travel expense to pick up the medication. While the cost of medications provided by pharmaceutical manufacturers helps to control chronic illness and reduce acute care expenditures, the cost to providers, clinic staff, and patients who use the PAPs reduces the total cost savings from PAPs.

Limitations

The first limitation is that the time and motion study was performed outside of normal business hours to (1) avoid interference with clinic operations and (2) isolate the time
actually necessary for performing the tasks related to fulfilling the requirements for PAP application, receipt, and distribution of drugs to patients. This method may underestimate the actual time required by clinic personnel to complete the work required by PAP facilitation for patients. Second, the staff member with the most experience in completing and submitting particular PAPs was observed, which would tend to underestimate the average time required if several staff members rather than a specific, experienced staff member were assigned responsibility for PAPs. Third, the medical assistant with experience in PAP applications had the lowest payroll cost among the professional staff in the clinic, and therefore our cost estimates would tend to be lower than would other medical clinics that use higher-cost professionals to provide PAP services.

Fourth, the time and motion observations were not performed by experts and included observation of only 1 medical assistant and should therefore be considered estimates. Fifth, the reliability of the time estimates is affected by the small number of observations—3 observations for the time estimates made in off-hours and a total of 10 observations for direct distribution time.

Conclusion

The number of PAP applications required per patient per medication per year has the greatest impact on clinic time and financial resources. The application submission method (i.e., mail, fax, or Internet) also influences the overall costs of providing this service in the clinic setting. Because of the variable number of PAP applications required by different drug manufacturers, medical clinics should base their decision to provide assistance with PAP applications on the time and associated costs over the course of 1 year and not on the 1-time application cost.

Acknowledgments

We acknowledge Craig Dietz, DO, Kansas City Free Health Clinic, Kansas City, MO; Melita Croom, PharmD, MPA, University of Missouri-Kansas City Drug Information Center, Kansas City, MO; Semaneh Wilkinson, PharmD, University of Kansas Medical Center, Kansas City, KS; and Kelly Buschler, BS, medical student, Kansas City University of Medicine and Biosciences, Kansas City, MO, for their support and assistance with this project.

Disclosures

No outside funding supported this study. The authors disclose no potential bias or conflict of interest relating to this article. Portions of this research were presented as a poster, “Cost of Providing Medications Via Prescription Assistance Programs to Medically Indigent Patients,” at a student session at the 49th Annual American Osteopathic Medical Association Meeting, October 25, 2005, in Orlando, FL (Abstract #91).

Author Patrick Clay served as principal author of the study. Study concept and design were contributed by Clay and author Stacy Mangum. Data collection was primarily the work of author Eric Vaught, with input from Mangum and Clay; data interpretation was primarily the work of Vaught, with input from Clay and author Alan Garos. Writing of the manuscript was the work of authors Daniel Hansen and Cameran C. Lindsey and Clay and Garos; its revision was the work of Hansen, Clay, and Lindsey.

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How Much “Spread” in AWP Pricing Is Unlawful?

A colorful ruling by federal U.S. District Court Judge Patti B. Saris (Boston) dated June 21, 2007, proclaimed that some pharmaceutical manufacturers had been “unscrupulously taking advantage of the flawed AWP (average wholesale price) system . . . by establishing secret mega-spreads far beyond the standard industry markup,” describing this behavior as “unethical and oppressive.” The case involved self- and physician-administered medications that “represent a tiny percentage of the thousands of pharmaceutical products available in the United States market.” Although manufacturers sold these medications to physicians and other providers for much less than AWP, plaintiffs, including third-party payers and patients who pay either coinsurance or full price for medications, paid for these drugs using AWP-based formulas. The resulting “spread” between the actual acquisition cost and reimbursed amount was so profitable for physicians that, the judge noted anecdotally, one doctor had a plaque that read, “This is the house that leucovorin built.”

After 20 days of trial and almost 40 witnesses, the judge concurred with plaintiffs that the drug companies took advantage of no oversight of self-reported AWP values and that “the published AWPs for defendants’ drugs are fictitious because they do not reflect the true average sales price (ASP) to providers, like doctors and pharmacists” (page 3). The judge noted in the decision, “I use the term ‘spread’ and ‘markup’ interchangeably” (page 3). She ordered AstraZeneca to pay damages of $4.45 million to non-Medicare third-party payers and Bristol-Myers Squibb (BMS) to pay damages of $183,000 for the period from December 1997 to December 2003. The judge ruled that Johnson & Johnson (J&J) did not violate the law because its “spread” to the physician to increase sales and market share.”

The ruling by Judge Saris highlights the difference between the plain meaning of AWP and the manner in which AWP has been used in the marketplace and even refers to AWP as “ain’t what’s paid.” Some managed care pharmacists have used this term for AWP for 10 years or more, particularly when referring to generic drugs and multiple-source brand drugs where the actual net purchase price bears no resemblance to AWP. Judge Saris found that while single-source drugs without generic competition bore a predictable relationship to acquisition costs, once these drugs faced generic competition, the “manufacturer could manipulate the spread—the difference between the actual selling price and the AWP-based reimbursement—to make the drugs more attractive to a physician,” and “could then ‘market the spread’ to the physician to increase sales and market share.”

Yet, even the invalid nature of AWP for single-source brand drugs became more clear to all by front-page news in October 2006 when it was disclosed that AWP is not based on a survey of the average of prices listed by various wholesalers.

So how much “spread” is too much? An interesting aspect of the decision in In Re Pharmaceutical Industry Average Wholesale Price Litigation is the method by which the spread between actual purchase and AWP was determined to be too much. A health care economist used the pricing history of single-source drugs that did not face competition to calculate the margin over his estimate of the ASP to health care providers that would be necessary to ensure a reasonable profit and cover administrative fees. A 30% margin was proclaimed to be the “threshold yardstick spread” and was also referred to in the ruling as the “speed limit” for single-source drugs during their period of exclusivity and for the first 6 months following generic launch. This economist concluded that the manufacturer is liable whenever the “speed limit” is exceeded. With respect to certain BMS products (Taxol, Vepesid injectable, Cytoxan injectable, Blenoxane, and Rubex) and one AstraZeneca product (Zoladex), Judge Saris found that AWPs “grossly exceeded actual physician acquisition costs” and that they “grossly exceeded the standard industry markup.” She also found that the two companies marketed “these mega-spreads between physician's acquisition costs and the AWP reimbursement benchmark in order to induce doctors to buy . . . based on the drugs' profitability.” In general, the ruling assigned damages based on spreads above the economist’s “speed limit” and requested additional analysis from the health insurance. Class 2 claims are from third-party payers in Massachusetts that reimburse Medicare beneficiaries for their statutory 20% coinsurance under Medigap or supplemental insurance. Class 3 claims included (1) all other third-party payers, (2) consumers who make coinsurance payments, and (3) consumers without insurance “for these drugs in Massachusetts and who pay for the drugs based on AWP”

This decision in In Re Pharmaceutical Industry Average Wholesale Price Litigation refers to “ perverse incentives” created by the Medicare system in basing provider reimbursement on AWP, unscrupulous behavior of “many pharmaceutical companies” in taking advantage of a “flawed AWP system” by acting “unfairly and deceptively by causing the publication of false and inflated average wholesale prices.” The ruling admonished third-party payers as “stuck” paying inflated prices since few have moved away from the AWP benchmark despite likely cost savings and despite Medicare’s lead in redefining the payment benchmark for Part B. The ruling hypothesizes that payers' inaction is due both to concern that providers will leave the network and that patients will be referred to more expensive hospital settings for drug administration.
Price manipulation claims are not new to the pharmaceutical industry. Almost exactly 4 years earlier, AstraZeneca announced on June 20, 2003, that it would pay $354.9 million and enter a 5-year corporate integrity agreement (CIA) to settle a federal inquiry into illegal sales and marketing of the prostate cancer treatment Zoladex. At the time, this was the second-largest settlement in history for improper sales and marketing by a pharmaceutical company. AstraZeneca pleaded guilty in federal district court to violating the Prescription Drug Marketing Act’s provisions forbidding the sale of drug samples and related promotional practices. According to the U.S. Department of Justice, the company had its employees provide thousands of free Zoladex samples to physicians, knowing that the doctors would prescribe the samples to patients and then bill Medicare and Medicaid for them; (2) offered free samples, unrestricted educational grants, business assistance, travel, entertainment, consulting services and honoraria to doctors in exchange for their prescriptions of Zoladex; (3) offered steep discounts to physicians for Zoladex without reflecting those discounts in AWPs reported to Medicare and Medicaid, thus inflating the prices and increasing physicians’ reimbursements; and (4) misreported and underpaid Medicaid rebates for Zoladex to the states under the Medicaid Rebate Program. The $355 million fine was distributed as $64 million for a criminal fine, $266 million to settle civil allegations, and $25 million to settle claims of overcharging Medicaid. The company had set aside $350 million in late 2002 to cover the anticipated settlement costs.


Differentiating Effective Data Mining
From Fishing, Trapping, and Cruelty to Numbers

Just Right or Too Much of a Good Thing?

It is said that politicians use statistics the way that an inebriated person uses a lamppost—"for support, not illumination." In managed care pharmacy today, some would argue that the same has become true of analyses of medical or pharmacy administrative claims data. The reasoning goes that, given a claims dataset and enough time to massage the data, one can set out to prove nearly anything and produce the desired answer. Is the accusation justified?

Compared with other types of research such as randomized controlled trials or patient surveys, retrospective analyses of administrative claims present greater potential for violations of ethical research standards. With a typical database and minimal effort, it is possible (not appropriate, but possible) to recalculate study results post hoc using seemingly endless combinations of methodological decisions. Some of the opportunities to revise study results, either for manipulation or legitimate scientific inquiry, include decisions about these questions:

- How many claims during what period of time constitute a drug user?
- How long is the washout period to define a “new start” with the medication?
- Which diagnosis codes in which positions (primary, secondary, tertiary) on how many medical claims constitute the appropriate inclusion criteria?
- For how long should patients be followed and continuous eligibility be required for inclusion in the sample?
- How should the researcher translate a broad concept, such as noncompliance or treatment success, into measurable decision rules?

So many study design changes are possible, all at the push of a computer key.

This ability to create multiple scenarios so easily has precipitated the lure of the “fishing expedition” in which repeated attempts are made to produce a particular desired finding. Unfortunately, this approach poses a substantial risk of generating incorrect information; while the resulting finding might be appealing, it might also represent nothing more than sampling error. A statistical significance standard of $P < 0.05$ refers to a 1 in 20 probability of “Type 1” error, falsely detecting a statistically significant result when outcomes are actually due to chance. After just 10 attempts using a statistical significance standard of $P < 0.05$, the probability of obtaining at least 1 false positive result is 40%. After 20 attempts, that probability increases to 65%.

However, the very feature of claims database research that is a major source of ethical and statistical shortcomings—the ready ability to perform post hoc analysis—is also a key tool in avoiding or mitigating those shortcomings. Used properly, for legitimate scientific inquiry and not to support a predetermined outcome of interest, post hoc analysis facilitates a candid and thorough presentation of study findings and ultimately a more useful research product. How to use this tool ethically and effectively is examined here, beginning with published examples of common problems in database analysis, and then turning to publications that illustrate “best practices.”

1. Common Problems in Claims Database Analysis

Boosting Academic Achievement With Refrigerators—Association Versus Cause and Effect

Sociologist James Coleman’s 1966 report on educational opportunity, which linked parental socioeconomic status to childhood academic achievement for the first time, has influenced educational policy in the United States for decades. But 5 years after the publication of Coleman’s work, a reanalysis of his data showed that knowing only whether a child’s household contained 9 common items (e.g., television set, refrigerator) produced a reasonably accurate prediction of the child’s verbal achievement (correlations of 0.72-0.80). Commenting on the reanalysis, statistician Elazar Pedhazur pointed out that no one would be so foolish as to purchase the 9 household items for all the underachieving children in the United States in an effort to boost their academic performance. Yet, he argued, many researchers fall into exactly the same trap when they mistake prediction—an association between two phenomena—for explanation—a cause-and-effect relationship. Pedhazur’s hypothetical naive researcher fails to understand that unmeasured causes, such as parental income, can influence both the purchase of household items and the achievement of children, thereby creating the appearance of a causal relationship where none exists.

Claims database research in managed care pharmacy is particularly vulnerable to confusion between association and causation. Studies documenting associations between suspected causal factors (e.g., a particular diagnosis, drug, or benefit design feature) and outcomes (e.g., compliance, cost, adverse event) are common, perhaps in part because they are relatively easy to perform. While there is nothing inherently wrong in documenting associations between events, trouble arises when researchers attribute causality to the associations, sometimes making policy recommendations based on the assumed causal mechanism, when cause-and-effect has not been shown or even explored. Two common examples of suboptimal practice are discussed below.

Cost of Illness(es)—All of Them

It is common and appropriate for claims database studies to assess the health care costs associated with particular disease states, often including measurement of total health care costs. But work of this type “crosses the line” when it ascribes total health care costs to a particular medical condition or treatment pattern (e.g., noncompliance, medication choice, diagnosis)
without examining whether the services used had any relationship to either the medication or the condition being treated.\textsuperscript{5-7}

One such analysis in the medical literature compared payers’ total (all-cause) health care costs for health plan enrollees with those without a diagnosis of atrial fibrillation (AFIB). Multivariate analysis and study design controlled for enrollee demographics, health plan, and other health conditions as measured by the Charlson Comorbidity Index (CCI). Notably, the authors removed conditions “that may have been caused by AFIB,” including heart failure and stroke, from the CCI; this decision left the health care cost analysis unadjusted for these conditions. The study found that AFIB patients had higher all-cause health care costs and higher rates of cardiovascular comorbidities than did plan enrollees who did not have AFIB. Without investigating the procedures associated with the increased health care service utilization, the authors described the $12,349 difference in per-person all-cause annual cost between enrollees with and without AFIB as the “direct cost burden” of AFIB. Similarly, without measuring cost change associated with AFIB treatment or comparing treated versus untreated AFIB cases, the authors concluded that “the successful treatment of AFIB may . . . have substantial health care cost savings benefits.”\textsuperscript{7}

Both conclusions were unfounded. On the basis of the work actually performed, one could appropriately conclude only that AFIB patients had more comorbidities and higher expenses. The degree to which AFIB caused the increased costs or comorbidities was not investigated. Since the AFIB patients had much higher rates of cardiovascular conditions, including heart failure (relative risk [RR] 29.6), other arrhythmias or conduction disorders (RR 16.9), heart attack (RR 8.5), and stroke (RR 6.6), it is not surprising that their total health care costs were higher. Thus, instead of being a causal agent producing higher costs, AFIB could have been a marker for heart disease severity, a consequence of the comorbid heart conditions such as stroke or heart attack, or a correlate of other unmeasured factors that were driving total health care cost. The conclusion that treating AFIB might substantially reduce total health care expense was not supported by study findings.

As we shall see from the “best practice” examples, a much more informative analysis could have been performed by sampling clinically homogenous groups and by examining the health care procedures used by AFIB and non-AFIB enrollees to assess how much of the additional cost was actually due to AFIB treatment. Notably, the AFIB study’s authors indicated that an investigation of the actual drivers of cost would “complete the cost picture of this condition” but described this analysis as “an area for future research.”

“Trapping” Explanations: Hinting at Causation Without Measuring It

A variation on the practice of describing association as causation is an approach in which the researcher hints, without actually measuring, that a particular feature of a drug or therapeutic class produces a specific outcome. One study from the medical literature examined the association between all-cause health services use and depression treatment consistent with “clinical guidelines” (from the Canadian Network for Mood and Anxiety Treatments [CANMAT])—including drug, dose, and duration. The recommended first-line drugs included all mechanisms of action: citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, bupropion, nefazadone, venlafaxine, moclobemide (monoamine oxidase inhibitor), and imipramine.\textsuperscript{8}

The authors concluded that greater guideline concordance was associated with increased visits to the prescribing physician, reduced inpatient admissions, and no significant differences in emergency room visits. Amazingly, neither medication side effects nor depressive symptoms were measured by the study, but the authors, consultants to pharmaceutical manufacturers, attributed study results to the side-effect profiles of the first-line medications that “may be more favourable than [those] of other antidepressants, which in turn increases patients’ adherence to medication thereby allowing them to receive the full benefit of antidepressant therapy.”\textsuperscript{8} Since the purported causal mechanism (reduced side effects producing better adherence and increased resolution of depressive symptoms) was not investigated, the conclusion that outcomes were attributable to this mechanism was unfounded.

This example of attributing outcomes to unmeasured attributes is depicted in Figure 1. Even without this obvious disconnect between cause and effect, the reader might be tipped to the flawed method by the inconsistency in the outcomes. Concordance with antidepressant “guidelines” was associated with reduced inpatient hospital use but not reduced emergency room visits.

2. Cruelty to Numbers in the Enchanted Forest of Statistics

“Torture numbers,” says writer Gregg Easterbrook, “and they’ll confess to anything.”\textsuperscript{1} In claims database analyses
employing retrospective designs, it is common for the groups being compared to differ in important ways. Covariates (predictive or explanatory factors) may be highly correlated with each other and with the study’s outcome measure(s). While these circumstances often require researchers to use multivariate statistical techniques, doing so without examining and providing additional basic information creates a kind of “enchanted forest of statistics”; an answer emerges from within, but no one knows exactly how it came about. In the worst-case “enchanted forest” scenario, readers are told that the analysis leads to a certain conclusion without being advised of the steps that led to that conclusion and have no way to interpret the practical importance of the findings. They may be left with the feeling that the numbers have been tortured, using incomprehensible and unexplained techniques, to produce the researchers’ desired conclusion.

An increasing number of “enchanted forest” examples are found in the burgeoning field of predictive modeling, developed to enable early identification and proactive intervention with high-risk patients.9 Because most predictive models are proprietary, their specific algorithms are typically unavailable in the published literature.9 Yet articles touting the benefits of these tools, often claiming remarkably high success rates and improvements over standard and published multivariate techniques, are common.10-12

One article from the published literature described many tasks necessary in analyzing medical data adequately (e.g., accounting for curvilinearity and skewness, categorical effects such as disease severity classification, and interaction effects) as outside the realm of standard techniques and therefore requiring the derivation of “a formula just like the regression technique, except that the formula is more complicated and more difficult to understand.”10 This assertion is questionable, since the effects discussed by the authors can be handled with techniques such as exponentiation, logarithmic transformation, dummy-variable coding, and interaction coding, which are interpretable using standard multivariate textbook methods. The article went on to claim that 34% of the variance in per-member-per-month (PMPM) medical charges could be explained with the authors’ proprietary tool, compared with about 10% to 15% for standard methods, without providing any details of the statistical analysis that produced this conclusion.10 It is not surprising that the predictive modeling field is currently the target of concerns about “black box” techniques.8

Concerns of this type are sometimes expressed about epidemiological studies as well. For example, a letter to the Lancet complained about the misleading use of risk ratios in the medical literature.13 The authors pointed out that changes in death rate from 2 to 1 per 100 and from 2 to 1 per 1,000 both represent relative risk reductions of 50%, yet clearly represent very different actual risk levels. They used findings of the Women’s Health Initiative (WHI) study as an example. Comparing a regimen of estrogen plus progestin versus placebo, the WHI had documented a hazard ratio of about 1 to 24 for invasive breast cancer, which one editorial had described as “a 24% increase in breast cancer risk.”14 But, as the authors of the Lancet letter pointed out, because the baseline risk of breast cancer was very low, the hazard ratio actually represented an incremental absolute risk of only about 0.49% over a 5- to 6-year follow-up, or about 0.09% per year.

3. Hey, Rocky—Watch Me Pull a Rabbit Out of My Hat!—Findings Without Foundation

Promised a rabbit, Rocky, the cartoon squirrel, was invariably disillusioned when his moose friend, Bullwinkle, instead produced another creature, which seemed to come out of nowhere. When methodological decisions do not build logically on an existing body of knowledge, consumers of research information may feel the same way as Rocky did. One British Medical Journal reader characterized the potential problem as a “Texas sharp shooter” effect.15 Just as an unscrupulous marksman might draw his target around the bullet holes that he already shot on the side of a barn, researchers who choose methodology post hoc, instead of a priori, risk misleading their audience. Failure to demonstrate foundation and a logical progression in claims database research gives the impression, whether real or only apparent, that the methods were drawn around the desired findings.

Knowingly developing procedures so that they will produce a desired outcome is obviously unethical, and the value of a priori decision making in producing valid research findings is clear. But the claims database researcher often encounters gray areas because of limitations of the claims themselves.

Sometimes Foundations Have to Shift (a Little): The Dilemma Posed by Claims Data Limitations

The claims database researcher who sets out to perform work based solely on a priori decision making may quickly encounter a tough reality: when claims databases are less than ideally suited for the task at hand, revisions to even the most carefully selected a priori techniques might become necessary. This situation arises mainly from 2 root causes.

First is variable quality of the information in the diagnosis fields. While some studies have documented a high level of accuracy in diagnosis fields of administrative claims data for common medical conditions such as asthma, respiratory infections, urinary tract infections, and acute myocardial infarction,16-18 it is clear that precision and straightforward interpretation are by no means guaranteed when using administrative claims as the data source. Even putting aside the possibility of misdiagnosis related to provider reimbursement levels, stigma, or diagnostic uncertainty,19,20 the codes appearing in administrative data may be unreliable or systematically biased for accurately diagnosed patients.21-23
In one study, 36% of the potential study population of type 2 diabetic patients had to be excluded from analysis because they also had 2 or more claims for type 1 diabetes in the same 1-year period. A comparison of medical records to database entries for primary care visits found that the administrative claims of accurately diagnosed patients contained a missing or incorrectly keyed primary diagnosis 34% of the time; secondary diagnoses were even less accurate.

A second cause of revised a priori methods is billing practices. Systematic coding issues can occur from the use of preprinted encounter forms, which typically precode the most common 20 to 30 diagnoses seen in the medical practice. Because the top diagnoses coded by specialty provider offices tend to be concentrated in a particular body system or medical condition, they are often coded more accurately and precisely than in primary-care provider or general-practitioner offices, where the encounter form codes must cover a wider range of conditions. Similarly, diagnoses tend to be more precise in inpatient than in outpatient billing because of differences in setting, attention to reimbursement levels, and coder training. Working with claims for specialty or injectable medications, an activity that is increasing because of greater use and cost for these drugs, can be particularly difficult. Because payers differ in billing requirements for biologic injectable medications, a multiple-payer dataset can contain different Health Care Financing Administration (HCFA, now known as the Centers for Medicare & Medicaid Services) Healthcare Common Procedural Coding System (HCPCS) codes for the same drug, as well as the same HCPCS code representing multiple drugs. For example, billing requirements posted in February 2006 for 1 payer assigned the same nonspecific “J” (injectable”) code (J3490) to adalimumab, efalizumab, exenatide, peginterferon alpha-2a, and peginterferon alpha-2b. “Home-grown” (payer-specific) codes are also possible.

For the claims database researcher, all this imprecision means that there is often more than 1 reasonable approach to methodological decisions, and it may take some trial and error to find the best approach. To ignore this need invites mistakes, such as examining the wrong diagnostic codes or studying a particular HCPCS code in the mistaken belief that it refers to a particular medication when the provider actually used the code to represent a different drug. And when a trial and error process becomes necessary, failing to mention it to consumers of research information gives unwarranted credence to the quality of the data and ultimately to the study results.

**Can Excessive Trust in Retrospective Database Analysis Compromise Patient Care?**

For those who believe that attention to the methodological and ethical hazards of claims database analysis represents esoteric fascination with picayune detail, the current status of chronic kidney disease (CKD) treatment provides sobering evidence to the contrary. As a recent *Journal of the American Medical Association* commentary discusses, many current CKD standards of care are based primarily on well-done observational analyses of epidemiological data. In light of new studies using stronger randomized designs, some treatment-to-outcome associations observed in older studies are now suspected to be due to unmeasured factors—just like the association between household appliances and childhood academic achievement in the Coleman reanalysis. The result is consternation and confusion as providers and promulgators of CKD care standards try to adjust to the newer and more accurate research information.

The moral of this cautionary tale is that claims database researchers risk promotion of suboptimal practice if they fail to measure and acknowledge the limitations of their work. Similarly, unless consumers of information adopt a “caveat emptor” attitude, they risk being subject to the intentional or unintentional biases of researchers. Both researchers and consumers must learn to recognize and use “best practices.”

**“Best Practice” in Claims Database Research: Knowing It When You See It**

“Best practice” work in claims database research is characterized by 4 hallmark features.

1. It goes beyond mere documentation that an association exists and instead investigates the specific nature and importance of that association.
2. It is utterly transparent about the number and type of analyses performed to reach study conclusions and reports completely all codes (diagnostic and procedural), details of the sample, and other information necessary to allow the work to be replicated by others.
3. It translates output from statistical analyses into terms that are understandable and useful to readers.
4. It investigates and candidly acknowledges the potential effects of ambiguities and limitations inherent in claims database analysis.

Following are some examples of “best practice” studies to illustrate the value of these approaches.

**Case Studies in Making Good Claims Database Research Better**

**Case Study #1: Appropriate Interpretation of Association Between Disease and Cost**

**Study Overview**

A study of the economic impact of anemia, conducted by Nissenson et al. and published in the *Journal of Managed Care Pharmacy (JMCP)* was similar in purpose to the aforementioned AFIB study but distinguished by 2 key methodological differences. First, its study population was limited to patients with diseases (CKD, human immunodeficiency virus, rheumatoid arthritis, inflammatory bowel disease, congestive heart failure, solid-tumor cancers) that predisposed them...
to anemia; thus, both of the study’s comparison groups had serious chronic illnesses. Second, in addition to calculating the payer’s all-cause health care costs for anemic versus nonanemic patients (controlling for demographics, coverage type, disease category, CCI), Nissenson et al. took a critical additional step in conducting a separate analysis of costs for medical services typically used in anemia management (e.g., transfusions, certain types of injections). They reported the percentage of patients using each anemia service for the sample overall and separately for each predisposing disease category. In a great example of transparency, they reported that services clearly attributable to anemia “accounted for only 5% to 11% of the cost differential between anemic and nonanemic patients.” The remaining costs were attributable to “services without an anemia diagnosis code or another unambiguous relationship to anemia.” The authors candidly acknowledged 2 possible explanations: (1) that the algorithm used to identify the anemia-related costs had failed to capture the full economic impact of the disorder, or (2) that anemia was a marker for underlying disease severity; that is, the association between anemia and cost was not causal.27

What Does Case Study #1 Show Us?

Appropriate caution in interpreting associations of the type observed in the AFIB study does not relegate hapless claims database researchers to pointing out cost differences, shrugging helplessly, and saying something like, “oh well, without medical records or a randomized trial there’s really no way to tell.” With reasonable effort and attention to good basic design, a claims database researcher can provide information that is both useful and consistent with the analyses performed.

Nissenson et al. created relatively homogeneous study groups by first sampling patients with serious chronic diseases, then subsampling to create comparison groups of patients with anemia and without anemia.27 The authors’ basic design controlled for measurable differences between study groups, but they acknowledged the possibility that unmeasured factors could have affected their results. They supplemented their primary analyses with a thorough investigation of anemia-related services, providing information about patterns of treatment for their patient population of interest. They documented the percentage of total health care costs clearly attributable to anemia. They reported completely all codes used in their analysis, enabling other researchers to replicate and perhaps improve on their methods. Finally, they were candid about the limitations of their work.

Case Study #2: Appropriate Interpretation of Association Between Program and Cost

Study Overview

A study of electronic prescribing conducted by McMullin et al. and published in JMCP examined the impact of a hand-held computerized decision support system that combined electronic prescribing capability with educational messages targeted to physicians.28 Outcome measures were costs PMPM and per new prescription. In addition to examining results in the aggregate (comparing patients of users with nonusers of the devices in a controlled trial design), the study authors assessed the same utilization outcomes for the subset of 8 therapeutic categories most often targeted by the messaging. The study found that use of the targeted medications declined from 39.4% to 35.8% in the intervention group and increased from 40.1% to 43.4% in the control group.

What Does Case Study #2 Show Us?

Even a strong design does not always eliminate the need for further investigation. In this instance, study authors used post hoc analysis to investigate whether the prescribing system’s educational messaging or other factors (e.g., just using the device itself, or a “Hawthorne effect” of participation in the project) produced the results observed in the controlled trial. By assessing whether the “dose” (the messaging) was related to the “response” (prescription cost), the study provided actionable information about electronic prescribing education, rather than an unexplained (and therefore less informative) association between the hand-held device and utilization outcomes.

Case Study #3: Design That Maximizes Explanatory Power of a Retrospective Analysis

Study Overview

An assessment of the impact of prescription drug coverage on spending for hospital and physician services in senior populations was conducted by Briesacher et al. in the context of discussion about the Medicare Prescription Drug, Improvement, and Modernization Act of 2003.29 This study’s purpose was to examine the accuracy of perceptions that providing seniors with drug coverage would result in improved access to necessary medications and ultimately lead to medical cost offsets.

The primary utilization outcome measures were expenditures for physician and hospital services. A fixed-effects panel model design was used to compare seniors who acquired drug coverage (“Gainers”) with those who remained without coverage during the study period (“Never”). In addition to the study’s primary analysis of change in aggregate health care spending for Gainers versus Nevers, Briesacher et al. performed an analysis of changes in spending on prescription drugs before and after the Gainers became eligible for drug coverage. The purpose of that analysis was to determine whether prescription drug use changed following the acquisition of coverage, thereby establishing “the mechanism by which drug coverage might influence medical care spending through increased use of medications.”27

Supplementing the basic panel model design, this secondary analysis was intended to provide an indication of whether any differences in medical expenditure patterns between the 2 study groups were actually due to the Gainers’ acquisition of drug
coverage and not to unmeasured differences between Gainers and Nevers. However, the study found that acquisition of drug coverage increased prescription drug spending without any consistent effect on medical expenditure.

What Does Case Study #3 Show Us?
In retrospective observational analyses, even with a strong basic design that includes appropriate comparator groups and solid statistical controls, it is possible for unmeasured factors to influence study outcomes. The authors of study #3 recognized this problem and took the critical step of looking for evidence that the factor of interest actually produced study outcomes, instead of making assumptions about unmeasured causal effects.

Case Study #4: Making Statistical Output Meaningful, Not Mysterious

Study Overview
In assessing the risk of cough with angiotensin-converting enzyme inhibitors (ACEIs) versus angiotensin receptor blockers (ARBs), the Agency for Health Research and Quality (AHRQ) applied an odds ratio derived from multivariate analyses (0.34 for odds of cough with ARBs compared with ACEIs) to a baseline cough rate of 8.9% for ACEIs based on clinical trials. The result (see Table 1), much more meaningful in practical terms than an odds ratio, was a number needed to treat (NNT): prevention of 1 ACEI-attributable cough would require treatment of approximately 18 patients with ARBs.

What Does Case Study #4 Show Us?
In addition to thoroughly documenting the methods used in its analysis, the AHRQ took the critical next step of translating the statistical output, an odds ratio, into clinically and practically meaningful terms.

Case Studies #5 and #6: Appropriate Adjustment to Unexpected Utilization Patterns

Study Overview: #5
In a study of Helicobacter pylori eradication regimens, researchers determined that a large number of patients filled prescriptions for antisecretionary medications before starting the H. pylori eradication regimen. Because it was impossible to determine from claims data alone whether the patients continued using the antisecretionary medications with the regimen, patients were classified into treatment categories both with and without the antisecretionary drugs, and results using the 2 methods were compared. Both methods yielded the same results.

Study Overview: #6
In an analysis of statin use after myocardial infarction, researchers discovered that cause of death was not available for a small number of cases in their administrative database. They calculated outcomes classifying the ambiguous cases in 3 different ways: as missing values, as cardiac deaths, and as noncardiac deaths. The results using all 3 methods were equivalent.

What Do Case Studies #5 and #6 Show Us?
The authors of both studies responded to unexpected circumstances by adjusting the original planned study methodology, comparing results using original and revised methods, and candidly reporting the results.

“Best Practice” Procedures
While it is impossible to enumerate here all the techniques that might be applicable to a given situation, there are practices that, if used consistently, will help distinguish appropriate from inappropriate claims database analysis. Researchers can follow these practices to help them engage in appropriate and effective data mining instead of falling victim to the lure of the fishing and trapping expedition. Consumers of information should look for evidence that researchers have followed these practices, and view results with suspicion when they have not.

1. Adopt an Appropriate Overall Approach
Researchers should understand and candidly acknowledge the limitations of claims databases and observational (rather than experimental) designs. Patients, health plan members, providers, and decision makers are poorly served when authors make more of their results than is warranted.

2. Build a Rational Basic Design
Researchers should begin the study design process with published information or other publicly available and accepted source(s) as the basis for initial methodological decision making. While designs employed in previous research (or logical variations thereof) are often a good starting point, various additional sources might be used. Classifications of drugs...
into comparison groups might be based on package labeling, as in a study of statin medications that stratified patients into "intensive" versus "standard" treatment based on whether product labeling indicated low-density lipoprotein cholesterol reduction of 40% or more for the drug and dosage combination.\[^{33}\] Classifications of patients might be based on statistical standards, as in a study of users of insulin lispro versus regular insulin, in which patients were grouped into quintile propensity score bins because of previous research documenting the effect of this stratification method on bias due to covariation.\[^{34}\]

### 3. Sail in Uncharted Waters When Necessary

Where no standard exists, it is also reasonable to state this and describe the rationale for the approach used. For example, the authors of a study of hypoglycemic events and costs in patients with type 2 diabetes acknowledged a lack of consensus in the literature with respect to washout times to define new starts; their choice of 4 months was based both on the literature and on known pharmacokinetics of drugs being studied.\[^{35}\] Similarly, in a study of the economic impact of herpes zoster (HZ), researchers noted difficulties in unequivocally attributing medical services to HZ because patients often present with vague pain symptoms, such as chest pain of unspecified etiology, up to a few weeks before diagnosis. Treating this problem as a study design issue, the authors included costs associated with these vague symptoms in their definition of HZ-related services, but compared patients diagnosed with HZ with a group of non-HZ patients, controlling for demographic and clinical factors.\[^{36}\]

### 4. Logically Connect Method to Objective

Researchers should measure outcomes that are logically related to the phenomenon of interest. In a cost of illness study, the primary outcome will likely be disease-associated costs, but note that a diagnosis for the disease need not be required. For example, a study of depression-related costs might include a separate assessment of services attributable to injury or overdose to account for the possibility that depressive symptoms would lead to self-injurious behavior.

To the extent that total costs are known to be affected by a particular disease, those should be measured, but clinical reasonableness and common sense will often dictate the removal of some costs. For example, in a study of the economic effects of antihypertensive compliance, it is clearly inappropriate to include costs for appendectomies in the outcome measure.

Timing may be important in these interpretations as well. For example, in a study of statin use for primary prevention, it would be inappropriate to attribute medical cost differences during the first month of treatment to better statin compliance.

### 5. Perform Sensitivity Analyses When Appropriate

Whatever methodological approaches are taken, sensitivity analyses of the effects of methodological choices are always helpful and often essential. For example, a study of hypoglycemic events in diabetic patients measured a key variable, hemoglobin A1C value, using 3 different methods (mean overall, last value, lowest value) and reported results using all 3 methods.\[^{37}\]

Numerous approaches to sensitivity analyses are possible. The key to conducting effective sensitivity analyses is to base them on reasonable scenarios and to be completely transparent with readers about the number of analyses performed. Transparency is essential because increasing the number of analyses also increases the probability of Type 1 (false positive) error.\[^{37}\]

### 6. Understand What Associations Do and Do Not Indicate

In interpreting associations between outcomes and other events or factors (e.g., benefit design features, medical condition, treatment), a good rule of thumb is that if an explanation for study findings is worth mentioning, it is worth investigating. If patients taking drug A have lower health care costs than patients taking drug B, a statement that this pattern is due to better medication compliance for drug A should be supported by evidence that (1) drug A’s compliance is better than drug B’s, and (2) better compliance is linked to lower health care costs.

Explorations of the process underlying an association do not replace the primary analyses documenting the association; they simply explore the association in sufficient detail so that conclusions are supportable. In technical terms, these explorations provide “construct validity,” that is, by assessing the mode of action underlying the outcome, they help document whether the study measures actually represent what the study authors believe they represent.\[^{38}\] For example, in the McMullin et al. study of the electronic prescribing system, the separate assessment of targeted drug categories provided evidence that differences between the study groups (users versus nonusers of the system) represented the effect of the system’s educational messaging (i.e., what the authors were trying to test), not only the effect of having the device or participating in the trial.

Some creativity is often necessary in devising methods to appropriately investigate associations and to measure the suspected causal relationships. For example, Figure 1 depicts the hinted conclusion in the aforementioned study of antidepressant “guidelines,”\[^{39}\] while Figure 2 depicts an alternative approach that includes measurement and testing of the suspected causal mechanism. Note that the authors of the antidepressant study did not classify medications by side-effect profiles other than to hint that CANMAT’s very diverse group of “first-line” drugs had more favorable side-effect profiles than other treatment choices had. However, in an actual test of the authors’ hinted explanation, classification of drugs by side-effect profile would be a necessary first step. Thus, in the alternative design, patients taking antidepressants with favorable and with less favorable side-effect profiles are contrasted. Patients taking benzodiazepines (the therapeutic class used by the majority of patients not receiving antidepressants in that study) serve as an
FIGURE 2  Alternative Measurable Study Design for Antidepressant Guideline Concordance Study

- Antidepressants With Favorable Side-Effect Profiles
- Antidepressants With Less Favorable Side-Effect Profiles
- Benzodiazepines
- ER Visits and Hospital Stays: Total (All-Cause)
- Depression/Anxiety Related
  - Compare Drugs by Therapeutic Class and Side-Effect Profile
  - Compare Adherent vs. Nonadherent Patients

Additional comparison group. Level of adherence to medication is a mediating (interim) outcome measure for the 2 antidepressant drug groups. For the final outcome measures, the analysis of all-cause costs is supplemented with a measure more logically related to the subject of the study—cost to treat depression and related conditions.

In most situations, the claims data are still available to the researchers after the initial analyses have been completed, making investigation of possible causal mechanisms feasible. Irrespective of whether the claims data are available, evidence from the research literature (e.g., similar studies conducted on other patient populations) should be assessed and, if appropriate, used as 1 component of the explanation of process. While it is unreasonable to expect investigation of every possible explanation, no matter how far-fetched, a reasonable expenditure of time to investigate major study findings should be expected of claims database researchers.

7. Use Disclosure Not Data Torture

The analytic process (and the data presentation) should begin with basic descriptive measures (e.g., percentage, mean, median, and a measure of dispersion such as range or standard deviation) for the study sample overall and for key subgroups. When used at the outset of the analytic process, basic descriptive information helps the researcher to select a statistical technique that is appropriate for the data. Additionally, readers can use this information to compare the study sample to their own populations on key dimensions (e.g., age, gender, comorbidities, benefit design) and determine the degree to which study results apply to them; that is, the “external validity” (pragmatic applicability) of the work outside its original setting.

Readers who are unfamiliar with the statistical techniques employed can better grasp the gist of the study findings from additional comparison group. Level of adherence to medication is a mediating (interim) outcome measure for the 2 antidepressant drug groups. For the final outcome measures, the analysis of all-cause costs is supplemented with a measure more logically related to the subject of the study—cost to treat depression and related conditions.

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8. Thoroughly Report Diagnosis, Procedure, and Drug Codes

To increase both the usefulness of the research and the reader’s confidence in its results, complete reporting of diagnostic, procedural, and prescription drug codes used in all phases of the research, including identification and classification of the study sample and calculation of all outcomes, is essential. The time period(s) for measurement of all codes should be reported clearly as well. Drug coding should address drugs dispensed in community and mail pharmacies and, if applicable, drugs administered in physician offices (e.g., injectables). If study results could be affected by incomplete or ambiguous information, for example, the lack of specific drug information for hospital stays or the difficulties in identifying newer injectable medications using HCPCS codes, this problem should be candidly reported and addressed either by sensitivity analyses or design modification(s).

Detecting and Managing Problems

Despite the best efforts of researchers to base their results on published criteria, previous work, or reasonable decision rules, problems commonly arise in claims database analyses, particularly when studying relatively new treatments or complex outcomes. Several approaches are helpful in detecting these shortcomings. To guard against engaging in an analytic
“fishing expedition,” it is best to perform these checks routinely and without first examining initial study results.

1. Verify Exclusion and Inclusion Criteria
First is an examination of cases or the individual claims excluded from a study sample or outcome measure. This examination provides some assurance that a code relevant to the outcome of interest, but used by providers in an unanticipated manner, is not overlooked. For example, if one of the outcome measures is hospitalization for a particular condition, it is helpful to run a frequency of diagnosis and procedure codes for hospital stays initially classified as being for other conditions. This step is particularly important when information about the payer’s reimbursement practices (e.g., use of “home-grown” codes or reimbursement limits for certain diagnoses) is unavailable or limited.

2. Account for Date-of-Service Ambiguities
The use of reasonable time windows can help account for uncertainty in claim dates of service due to common billing practices. For example, in a study of practice patterns in management of upper gastrointestinal symptoms, researchers assessed the effect of moving dates of diagnostic tests backwards (earlier) by 2 days to allow for situations in which the physician received laboratory test results by telephone before the claim date.52

3. Consult an Independent Third Party
A consultation with 1 or more colleagues may become necessary in situations in which a methodological decision makes a difference in the study results and there is no definitive information available to guide the decision. To avoid “fishing” or “Texas sharp shooting,” it is important to keep the colleague uninformed about the implications of his/her judgment for study findings. A reasonable approach is to explain the purpose of the study, present the methodological choices, and briefly review the methodological rationale underlying each one, without advising the colleague of the results obtained using each method. However, such a consultation should not be used as an excuse for failing to share information with readers; situations of this type should be documented as part of any presentations or papers written about the study.

4. Review Individual Claims for a Validity Check
Finally, after completing an administrative claims analysis according to a predetermined plan, it is wise practice to take time to look at the claims histories for a sample of patients. Did the methodology seem to classify the patients appropriately? Were any important details missed? It is not uncommon to discover when looking at claims for a sample of patients that a specification was missed in translating the study design into codes on the claims. For example, if patients are classified as having a hospitalization for a particular condition (e.g., ulcer disease), it is informative to look at a sample of the patients with hospitalizations, carefully examining the diagnoses and procedure codes for evidence that the classification makes sense (e.g., for procedures like endoscopies or other gastrointestinal procedures).

### Finding Your Way Through the Enchanted Forest: The Role of Reviewers and Readers
The procedures and approaches described above should be routine in research with administrative claims. Researchers should be truthful and transparent in presenting methods and results and let readers decide for themselves if they agree with the interpretations. This suggestion is not novel, of course, but it is becoming increasingly important as multivariate statistical techniques become increasingly complex and esoteric and competition for scarce health care resources intensifies.

What do we at JMCP look for in claims database research? What should readers look for? A summary checklist of “best practices” is in Table 2. “Danger signs” that these practices were not followed include the following:

1. Methodological decisions are unexplained or inconsistent with previously published research without an identifiable reason or explanation by the authors.
2. More than 1 approach to a key methodological decision

### Table 2 Checklist of Best Practices for Claims Database Research

<table>
<thead>
<tr>
<th>Associations</th>
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<tbody>
<tr>
<td>• Process (mode of action linking 1 factor to another) was investigated, if possible, and is clearly described.</td>
</tr>
<tr>
<td>• Description of factor(s) as causal was tested in analysis (ideal) or is supported by another method, such as literature review.</td>
</tr>
<tr>
<td>• The degree to which the suspected causal mechanism does or does not explain the outcome is reported honestly.</td>
</tr>
<tr>
<td>• The logical relationship between study findings and policy recommendations is clear.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Data Analysis and Data Presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Basic descriptive statistics, including percentages, counts, and measures of central tendency and dispersion are presented.</td>
</tr>
<tr>
<td>• Discrepancies between descriptive and multivariate statistics have been investigated and are explained.</td>
</tr>
<tr>
<td>• Statistical outcomes are translated into quantitative expressions of value (e.g., absolute risk reduction, number needed to treat) using standards described in JMCP author guidelines, and into practical terms understandable to readers.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Research Process</th>
</tr>
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<tbody>
<tr>
<td>• Initial methodological decisions are based on published source(s) or logical variations thereof.</td>
</tr>
<tr>
<td>• Rationale for modifications to initial study design is described clearly.</td>
</tr>
<tr>
<td>• When more than 1 methodological approach is reasonable, sensitivity analyses document the effect of decisions on study results.</td>
</tr>
<tr>
<td>• All codes and date ranges used in identifying the sample or calculating outcomes are reported in complete detail.</td>
</tr>
</tbody>
</table>
would have been reasonable, but the authors have neither explained their choice nor provided appropriate sensitivity analyses.

3. The authors do not disclose the methods used to identify the study population or outcome(s) in sufficient detail to allow replication of the research by others.

4. Descriptive statistical analyses are either missing or do not contain appropriate details (depending on the analysis, these might include mean, median, minimum, maximum, standard deviation, or interquartile range) critical to a basic understanding of the study population and the methods.

5. Policy recommendations are not supported by study results.

Authors whose work displays any of these warning signs can expect additional questioning and scrutiny from JMCP editorial review, in service of the journal’s goal of providing readers with valid, reliable, and useful information.

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DISCLOSURES
The author discloses no potential bias or conflict of interest relating to this article.

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Editorial

Letters to the Editor

JMCP welcomes letters that serve to clarify subjects published in previous issues of the Journal or regarding subject matter of interest to managed care pharmacists. Letters in JMCP are not peer reviewed but are subjected to editorial review. Letters should be prepared in a word processing program, preferably Microsoft Word, and submitted electronically at jmcp.msubmit.net. See www.amcp.org for details.
To the Editor:

We read with interest the article by Yokoyama et al. (April 2007 issue of JMCP) on the effects of a step-therapy program for angiotensin receptor blockers (ARBs) on antihypertensive medication utilization patterns and the cost of drug therapy. The authors reported a saving of $0.03 per member per month with step-therapy intervention that required the use of an angiotensin-converting enzyme inhibitor (ACEI) prior to an ARB in a health plan population of approximately 1 million. However, we have found the conclusions in the study, as well as the editorial, unbalanced and troubling for several reasons.

First, there were several limitations of the study design that would clearly impact the cost-saving results. The authors did outline the limitations. These included the potential costs of member and provider dissatisfaction, pharmacy and prescriber costs associated with requesting a prior authorization or changing to an ARB antihypertensive alternative, costs incurred in visits to the physician to switch therapy, and administrative and resource costs required to run the intervention program. In addition, there were pharmacy costs associated with explaining claim rejections to patients. However, not enough emphasis in the manuscript or accompanying editorial was placed on the fact that rebate contracts on drug costs were not factored into the cost analysis. These significant rebates would neutralize the apparent cost savings for a step-therapy managed care intervention program outlined in this manuscript. This analysis would have helped to present a more balanced case for your readers.

Another factor not addressed satisfactorily in the article was the finding that, of the 1,296 patients who attempted to obtain an ARB under the step-therapy intervention, 6.6% did not receive any antihypertensive therapy within 12 months of the index date. Not taking therapy certainly will save money in the short term, but was stopping antihypertensive medication medically and ethically appropriate for these patients? What was their clinical outcome, and were costs incurred for later cardiovascular medications/interventions? Only pharmacy claims data were considered in the article, and the effects of step-therapy intervention on clinical outcomes, including effective blood pressure (BP) control and/or attainment of the JNC 7 (Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure) BP goal were excluded.

Perhaps more alarming was the accompanying editorial to this article. We have identified several troubling statements and examples of selective literature citing; we have listed a sample below:

- The editorial downplays the limitations of the analysis. Despite the manuscript noting many factors that would negatively impact the apparent cost savings, the editorial claims that the savings are “underestimated.”
- The editorial incorrectly cites a draft report from the Agency for Health Research and Quality (AHRQ), “Comparative long-term benefits and harms of ACEIs versus ARBs for treating hypertension,” ignoring reported differences in BP efficacy and medication persistence between ACEI and ARBs. The report states that there are significant differences in several assessments, including BP lowering, frequency of cough, and persistence. This is perhaps an irrelevant point, since this report is only at the draft stage and has serious limitations that still need to be addressed before it is finalized.
- The editorial questions the long-term safety of ARBs, citing the AHRQ report. However, the report conclusions regarding long-term differences between ACEIs and ARBs are severely limited by the duration and quality of the studies included, with nearly 70% being of 6 months’ duration or less.
- The report analyses assume that agents within a class are equivalent (i.e., a class effect) and, therefore, minimize differences among the individual agents and disregard evidence-based medicine. For example, both candesartan and irbesartan have demonstrated greater BP-lowering efficacy over losartan in 2 well-controlled clinical studies at maximum doses, meeting stringent U.S. Food and Drug Administration requirements for superiority claims.
- The editorial selectively cites literature on medication adherence for patients receiving ACEIs. Several studies that were not cited in the editorial demonstrate significantly higher compliance and lower discontinuation rates with ARBs compared with ACEIs. Compliance and adherence are recognized cost drivers for managed health care.

An important point that should be taken into account is that clinical studies with ARBs are more recent than studies with ACEIs, which were conducted in the 1990s, when the prevalence of metabolic syndrome and type 2 diabetes mellitus was considerably less in the United States. There are now data with ARBs in “difficult-to-treat” hypertensive patients that cannot be extrapolated to the older studies with ACEIs in a less severe hypertensive population. In addition, the change in population risk, with higher failure rates with monotherapy and differences in compliance, make the cost estimates unrealistic.

Hypertension control continues to be a tremendous unmet medical need in the United States, with approximately two thirds of the 72 million Americans with high blood pressure not meeting recommended target blood pressure goals. ARBs and ACEIs are integral medications in the antihypertensive armamentarium. Although both drug classes inhibit the renin-angiotensin aldosterone system, important clinical differences exist between the classes as well as within each class that are important for physicians to consider when trying to optimize care for individual patients. In light of the asymptomatic nature of hypertension and often lifelong duration of therapy for individuals who have high blood pressure, artificially limiting the important treatment choices for physicians and patients
Letters

should not be encouraged; decisions as critical as these deserve responsible, well-balanced analyses and careful, thorough review of the available evidence.

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DISCLOSURES
C. Venkata S. Ram and Thomas Giles attest to having no conflicts of interest, including consulting work or receipt of research grants or compensation from pharmaceutical manufacturers.

REFERENCES

The Authors Respond:
Ram and Giles raised concern about the impact of rebates on net drug cost and program savings. While there would be a loss in manufacturer rebates for the formulary angiotensin receptor blockers (ARBs), these offsets were considered before the step-therapy program was implemented. Rebates would only apply to select ARBs, and at the time of the study, net costs of these agents, including rebates, were higher than the cost of generic angiotensin-converting enzyme inhibitors (ACEIs). Regarding Ram and Giles comment on the 6.6% of patients who did not receive any antihypertensive therapy within 12 months of the index date, this finding is consistent with analyses of other step-therapy programs as discussed in the article.1 More recently, evaluation of an ARB step-therapy program at BlueCross BlueShield of Texas by Gleason et al., presented at the Academy of Managed Care 19th Annual Meeting & Showcase, found that 8.8% of members had no antihypertensive claim in at least 4 months of follow-up.2

Although we acknowledge there are limitations in the analysis that were properly addressed, we believe the findings are credible and useful for decision making.

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DISCLOSURES
The author discloses that she completed a fellowship with Novartis Pharmaceuticals Corporation, sponsor of the research discussed in her JMCP article.

REFERENCES

The Editors Respond:
We welcome the opinions of Ram and Giles regarding angiotensin receptor blocker (ARB) step-therapy interventions. In general, step-therapy interventions are becoming increasingly common in administration of pharmacy benefits in the United States. The proportion of large employers with step-therapy edits doubled from 22% in 2000 to 44% in 2004.1 For the 12-month period through September 30, 2004, step-therapy protocols were reported by 85% of health maintenance organizations,
Letters

two thirds of preferred provider organizations, 79% of Medicaid plans, and about one half of Medicare-risk plans. Hence, there is increasing need to measure clinical, service, and cost outcomes of these interventions, the principal point of the editorial by Curtiss in which a categorical system to rate step-therapy interventions by the degree of restrictiveness was proposed. This categorical system would clearly define the step-therapy intervention according to variables such as the number of first-line therapies required and the scope and method of attestation required of the prescribers.

Regarding specific concerns, Ram and Giles claim that insufficient attention was paid to the effects of rebates on drug cost savings associated with the ARB step-therapy intervention evaluated by Yokoyama et al. Presumably this criticism also applies to Gleason, who reported in the same issue of JMCP even larger drug cost savings from a separate ARB step-therapy intervention. Of note, Yokoyama included the limitation that rebate contracts could offset some of the estimated drug cost savings. Curtiss, in his editorial, did not mention drug manufacturer rebates because these contracts with pharmacy benefit managers and health plans for ARBs acknowledge and allow the widespread use of step-therapy interventions that require prior use with an angiotensin-converting enzyme inhibitor (ACEI). Hence, a rebate of 20%, for example, on ARBs with a typical managed care price of $2.00 per day of therapy still leaves a gap of about $1.40 per day compared with a generic ACEI such as generic benazepril that has a managed care price of $0.40 per day or less. This means that 4 to 5 patients can be treated with a generic ACEI for the cost of treating 1 patient with an ARB. And, of course, from the patient viewpoint, these rebate contracts provide no compensation to members forced to pay higher copayments for brand drugs compared with generic drugs.

We do agree with Ram and Giles that not taking a drug will produce drug cost savings in the short term, and while we are also curious about the outcomes for the 6.6% of patients who did not receive any antihypertensive therapy within 12 months of the step-therapy intervention, this proportion seems small in the context of results of antihypertensive medication adherence studies. Fewer than 50% of even high-risk patients are adherent on both antihypertensive and lipid-modifying drugs within 3 months of starting drug therapy and only about one third at 6 months.

Third, Ram and Giles cast doubt on the assertion that savings from the step-therapy intervention were underestimated. However, the possibility of underestimation of savings is quite clear. Since Yokoyama et al.’s study sample was drawn for only a 6-month period, a program run for a full year would likely have been applied to many more patients, producing additional cost savings. Additionally, Yokoyama et al.’s study sample was limited to continuously enrolled members, who represented only 76% of the patient population to which the program was actually applied.

Fourth, the editorial is accused of ignoring differences in blood pressure reduction efficacy. One is hard-pressed to find better evidence than independent, expert systematic review of all of the available evidence, and to quote from page 31 of the Agency for Health Research and Quality (AHRQ) executive summary, “(o)verall, there was no clear difference in the blood pressure lowering efficacy between the two classes of agents, no matter what criteria were used for study inclusion. Because of the heterogeneity in study protocols, quantitative meta-analysis was not performed.” Although no systematic review is flawless, the U.S. government AHRQ evidence reviews are widely respected in most evidence-based medicine circles as one of the least biased, most inclusive, and most accurate reports available. For Ram and Giles to selectively scoop a few studies from the mass of heterogeneous data reflects a narrow approach; in this case, the forest should be appreciated over the trees.

Although clinical differences may exist within each class particularly with respect to U.S. Food and Drug Administration-approved indications (some agents are indicated for hypertension alone while others have additional renal or cardiac indications), the clinical profiles sufficiently overlap for the ARBs and ACEIs to validate step-therapy in the absence of individual medical necessity. As noted in the AHRQ report (page 11), “The hypothesis that ACEIs and ARBs have clinically meaningful differences in long-term outcomes in individuals with essential hypertension is not strongly supported by the available evidence.” Added to the thorough evaluation of evidence presented in the AHRQ report on comparative effectiveness are the results of retrospective analyses such as Winkelmeyer et al. who found multivariate-adjusted 1-year mortality that was not different between ARB and ACEI users among 14,190 Medicare beneficiaries who received either an ACEI or ARB within 90 days of a myocardial infarction (hazard ratio, 1.04; 95% confidence interval (CI), 0.88-1.22). Regarding the complaint by Ram and Giles that the AHRQ report is presently available only in “draft” form, this is the customary procedure for AHRQ, and readers might consider the confirmatory conclusion from the final 2006 version of the NICE (National Institute for Health and Clinical Excellence) guidelines for hypertension treatment (page 18): “the GDG (guideline development group) felt that the benefits from ACEIs and angiotensin-II receptor antagonists were closely correlated and that they should be treated as equal in terms of efficacy (although, because of cost differences, ACEIs should be initiated first).”

It is true that adherence and persistence with antihypertensive therapy are necessary to realize the anticipated efficacy as measured by intermediate outcomes such as blood pressure reduction as well as the hard endpoints of myocardial infarction and cardiovascular-related death. Ram and Giles prefer studies to support a claim of superior adherence with ARBs, one a study by Koylan et al. conducted in Turkey that was an outlier among the 17 studies evaluated in the AHRQ report on
comparative effectiveness.\textsuperscript{11} The AHRQ report at page 43 concluded, “With the possible exception of the study by Koylan et al., adherence with ACEIs and ARBs was similar (Table 7).” In the second study cited by Ram and Giles, the lisinopril (ACEI) group had a higher severity of illness and greater use of concurrent medication such as antihyperlipidemics, antiplatelet agents, and beta-blockers compared with the valsartan (ARB) group, and the adjusted adherence was statistically significant but not practically significant, 89.9% for lisinopril (95% CI, 89.3%-90.6%) versus 90.1% for valsartan (95% CI, 89.0-91.1%).\textsuperscript{12}

For those who prefer trees rather than the forest, we recommend reading the 72 studies referenced in the 57-page AHRQ report on comparative effectiveness of ACEIs and ARBs and the 79 studies referenced in the 98-page NICE hypertension guideline; ACEIs and ARBs are clinically sufficiently similar to allow step therapy. Artificially limiting clinicians’ ability to care for patients by selectively citing literature should be roundly condemned by all; likewise, selectively citing contrary outlier literature to support frivolous expenditure on costly medication that fails to provide unique benefits should be also be denounced in the public forum.

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Frederic R. Curtiss, PhD, RPh, CEBS
Editor-in-Chief
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6. Personal communication with an officer of a pharmacy benefits management company.


The Hickory Project Builds on the Asheville Project—An Example of Community-Based Diabetes Care Management

To the Editor:

We read with interest the recent JMCP commentary calling for managed care organizations (MCOs) and community pharmacies to seize the opportunity to work together in chronic care and disease management.\textsuperscript{1} Your readers may be interested in the Hickory Project, a disease management partnership developed to demonstrate the value of using community pharmacists and nurse practitioners as care managers to improve quality measures and positively impact patient health outcomes in Hickory, North Carolina, and the surrounding area. This combined effort includes the coordinating services of American Health Care (AHC), a pharmacy benefit manager and disease management company, and brings together Wells Fargo Insurance Services, community pharmacists, nurses, physicians, and support staff. One of the key functions of AHC is to integrate medical and pharmacy data for patients with diabetes who are enrolled in the disease management program. Lessons learned from the Asheville Project, also in North Carolina, are incorporated into the Hickory Project.

Pharmacists and nurse practitioners in the local community are recruited and held responsible for direct patient contact (to coach, encourage, and educate the patients) with a goal of achieving improved patient care and quality measures as outlined by a patient’s physician and national guidelines. This project involves 9 independent community pharmacies, 7 nurse practitioner clinics, and AHC. Trained clinical professionals meet with each patient each month to provide education and monitor health progress. The patient’s weight and blood pressure are documented at each meeting, and lab values, self-monitoring blood glucose tests, and medications are reviewed. All interactions are recorded on a patient progress summary...
form that is used to coordinate data between the patient and health care team members.

The first phase of this community-based patient care project was to organize a working procedure between AHC and the network of community pharmacists—and in some areas, nurse practitioners. The local pharmacists were recruited and disease-specific training sessions were provided. Disease-specific training was conducted through a combination of a Web-based program and fax transmissions. Successful completion of three 2.5-hour training sessions, followed by an examination of covered materials, conferred accreditation by AHC on the pharmacist as a “Hickory Project care manager.” The total training time for certification was approximately 9 hours.

The training provided to the Hickory Project care managers was conducted to update them on the latest national guidelines and protocols for diabetes management. (Six nurse practitioners involved in the Hickory Project were not required to go through training because of their existing expertise in diabetes care management.) As of December 2006, 23 pharmacists had completed the training. An informal survey of the pharmacists revealed a high level of professionalism and a desire to be involved in a community-wide effort.

The value of community pharmacists in the delivery of disease management programs has already been successfully demonstrated in the Asheville Project. The Asheville Project, started in 1996, is a disease management program in which 2 large self-employed insurers in North Carolina offer services to employees, dependents, and retirees by community pharmacists for chronic disease states such as diabetes, asthma, and depression. The Asheville Project shows that patients with diabetes who participate in this long-term pharmaceutical care program use fewer sick days and achieve lower hemoglobin A1C levels as well as improved lipid levels, while employers have experienced a decline in mean total direct medical costs. Physicians working with the Asheville Project pharmacists have been pleased with the quality of patient care and have seen firsthand the benefits of a coordinated collegial team effort in chronic disease state management. Because of monthly monitoring by the local pharmacist care managers, valuable physician time is saved, patient deficiencies are corrected, and complications are averted.

The need for quality disease management was summed up in a statement by the National Committee for Quality Assurance: “The fact that many Americans do not receive appropriate preventive care and care for chronic conditions like diabetes and hypertension also means that annually there are thousands of preventable second heart attacks, kidney failures, and other conditions such as painful and debilitating fractures from osteoporosis.” Several recent studies demonstrate that a handful of such conditions account for more than half of U.S. medical costs. As reported in The State of Health Care Quality 2004, more than $9 billion is lost in productivity and nearly $2 billion is incurred in hospital costs that could be avoided through more consistent delivery of best-practice care. “More than 14,000 heart attacks and strokes could be prevented each year through better diabetes management alone (A1C control).”

Fred Eckel, who reviewed the Asheville Project, stated, “Based on our Asheville experience, it is apparent to us that disease management, or health management programs as I prefer to call them, will best be accomplished through local initiatives. Eventually, regional or national employers or payers may get into the act; but our greatest success will come through local projects.” To be successful, these local initiatives need to have answers to the questions regarding compensation of pharmacists for their services and “what’s in it for me” for patients, physicians, pharmacists, and employers.

The Hickory Project identified prospective patients through analysis of medical and pharmacy claims, and these patients were invited to participate via employer information sessions and direct mailings on disease management. The patients who chose to be a part of the disease management program received reduced copayments or had copayment waiver for their management-related medications. Each patient was assigned a care manager who provided current medical and pharmacy claims data from AHC. The care manager was a local community pharmacist in most cases, and the reduced or waived copayments remained in effect for as long as the patient complied with scheduled appointments with the care manager. Patients received disease-specific information, a list of quality measures associated with their disease state (e.g., goals for A1C, blood pressure, and low-density lipoprotein cholesterol), and educational materials to instruct and encourage them about the importance of knowing and attaining each quality measure.

Most pharmacists would love to spend more time with patients, but they would quickly go out of business if they spent 15 minutes with every patient who had a chronic condition. The Hickory Project paid $30 to the pharmacy for every initial face-to-face pharmacist consultation with an enrolled patient (the sessions were anticipated to last about 30 minutes); each 15-minute follow-up visit was compensated at the rate of $15. Analysis of the adequacy of this compensation has not yet been conducted. Patient consultations are held in privately designated areas in the pharmacy.

New patients are assigned to the certified care managers, and the option of mail-order prescriptions was eliminated to facilitate more effective face-to-face interaction between the patient and the care manager. Most patients in the project receive their prescriptions from their pharmacy’s care managers. The care managers receive a patient progress report each month from AHC via fax transmission that details the assigned patient’s medical and pharmacy data and any deficiencies in quality measures. (The fax transmission of information is being replaced by an online, Web-based, interactive system accessible to the care team members.) This monthly updated patient record
follows the progression of care and patient assessments and is forwarded to the attending physician as a precise record of goals met and goals needing improvement.

Patients also receive a "to do" list after each care manager appointment. The care manager talks to each patient about the importance of daily exercise, good nutritional eating habits, and the dangers of smoking; encourages the patient when it is time to see the physician; discusses needed lab tests; and reminds the patient to talk to a physician about specific quality measures needing attention.

The first employer group to sign on with the Hickory Project was the Hickory Springs Manufacturing Company, based in Hickory, North Carolina, and one of the nation's largest manufacturers of furniture (with 5,910 employees). Hickory Springs Manufacturing Company implemented this program, in part, on the basis of the reported success of the Asheville Project and to evaluate the financial results and health outcomes associated with a similar intervention for its own employees.

Baseline Measures

The following baseline findings were generated from an evaluation of the beneficiaries of 3 local employers interested in the Hickory Project before participant enrollment in the disease management project. From medical and pharmacy data, the need for such a project was confirmed. For the year 2005, 566 patients among these 3 employer-sponsored groups had an International Classification of Diseases, Ninth Revision, Clinical Modification code of diabetes (250). This correlates to a prevalence of 6.1%, based on the 9,282 total covered members included in the sample. Of those diagnosed members, 509 (89.9%) were taking antidiabetic medication, which included 448 members older than 40 years.

- 49.8% of these older members (223 members) were taking some type of lipid-lowering medication
- 56.3% (252 members) were self-testing blood glucose (STBG)
- 32.5% (146 members) were identified as having had a lipid panel performed within the 1-year period prior to participant enrollment
- 50.4% (226 members) received at least 1 A1C test
- 59.4% (266 members) were taking blood pressure medications

Six-Month Findings for the Hickory Springs Manufacturing Company

As of May 15, 2007, the Hickory Project had enrolled 134 members with diabetes (see table). Preliminary findings after the first 6 months for the initial group of 20 patients enrolled in November 2006 showed some improvement in blood pressure, A1C values, annual eye exams, and STBG, but opportunities to improve quality remain.

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**TABLE Six-Month Data for First Group of 20 Enrolled Patients**

<table>
<thead>
<tr>
<th>Quality Measure</th>
<th>No. of Members (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A1C</strong></td>
<td></td>
</tr>
<tr>
<td>Below 7.0% at enrollment</td>
<td>8 (40)</td>
</tr>
<tr>
<td>Below 7.0% at 6 months</td>
<td>12 (60)</td>
</tr>
<tr>
<td><strong>Blood pressure</strong></td>
<td></td>
</tr>
<tr>
<td>Below 130/80 mm Hg at enrollment</td>
<td>5 (25)</td>
</tr>
<tr>
<td>Below 130/80 mm Hg at 6 months</td>
<td>10 (50)</td>
</tr>
<tr>
<td><strong>Blood glucose testing</strong></td>
<td></td>
</tr>
<tr>
<td>Self-test daily at enrollment</td>
<td>14 (70)</td>
</tr>
<tr>
<td>Self-test daily at 6 months</td>
<td>19 (95)</td>
</tr>
<tr>
<td><strong>Annual eye examination</strong></td>
<td></td>
</tr>
<tr>
<td>Within previous 12 months at enrollment</td>
<td>10 (50)</td>
</tr>
<tr>
<td>Within previous 12 months at 6 months</td>
<td>13 (65)</td>
</tr>
</tbody>
</table>

A1C = hemoglobin A1C.

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**DISCLOSURES**

The authors disclose no potential bias or conflict of interest relating to this letter.

**REFERENCES**


Thanks to

**JMCP Peer Reviewers, January–June 2007**

Each of the following Peer Reviewers contributed one or more reviews of manuscripts submitted to the *Journal of Managed Care Pharmacy* in the first half of calendar year 2007. We are indebted to these professionals for their assistance in continuous quality improvement of the content of *JMCP*.

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AMCP recognizes those who share our vision with peers as its AMCP Visionaries.

- **AMCP Visionary**
  Those recruiting one to three new members will be recognized each month in the *AMCP News*, posted on the AMCP website, and listed in the *Year in Review*

- **Four to Seven Referrals: Sapphire Level**
  In addition to the above, Sapphire Visionaries will be recognized at AMCP conferences with a special ribbon to attach to their meeting badge

- **Eight to Fourteen Referrals: Ruby Level**
  In addition to the above, Ruby Visionaries will receive a ruby lapel pin and a personal letter of thanks from the AMCP president

- **Fifteen to Twenty-Four Referrals: Emerald Level**
  In addition to above, Emerald Visionaries will receive an emerald lapel pin and a certificate of appreciation presented at the AMCP Leadership Luncheon during the Annual Meeting

- **More Than Twenty-Five Referrals: Diamond Level**
  In addition to the above, Diamond Visionaries will receive a diamond lapel pin and an invitation to attend the gala Awards Dinner held during the Annual Meeting each spring

See the AMCP website for membership applications and additional information, www.amcp.org
Boston

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AMCP
Academy of Managed Care Pharmacy
Thursday General Session — Christopher Gardner

Surmounting acute obstacles on his road to success, the amazing story of Gardner’s life was published as an autobiography, *The Pursuit of Happyness*, and inspired the Columbia Pictures’ movie of the same title, starring Will Smith.

Always hard-working and tenacious, a series of circumstances in the early 1980s left Gardner homeless in San Francisco and the sole guardian of his toddler son. Unwilling to give up Chris Jr. or his dream of financial independence, Gardner started at the bottom. Without connections or a college degree, he earned as pot in the Dean Witter Reynolds training program.

Often spending his nights in a church shelter or the bathroom of a Bay Area Rapid Transit station in Oakland, Gardner was the sole trainee offered a job at Dean Witter Reynolds in 1981. He spent 1983–1987 at Bear Stearns & Co., where he became a top earner, and then in 1987, he founded the brokerage firm Gardner Rich & Co. in Chicago.

Friday General Session — Regina Herzlinger, PhD

One of the most significant voices in health care reform today, Regina Herzlinger is known as the “Godmother” of consumer-driven health care — a term she coined and a movement she helped create.

An important researcher and analyst, she was an early predictor of the unraveling of managed care. Her solutions for structuring, financing and delivering health care are innovative, yet commonsensical.

Herzlinger has written three books on health care reform, including most recently, *Who Killed Health Care? America’s $2 Trillion Medical Problem — and the Consumer-Driven Cure*. This book is more than just an assault on the forces that are driving health care costs, driving down the number of people who are covered, and degrading patient care. It is also a manifesto, a powerful argument for consumer-driven reforms that already are transforming the system.

She is the first woman to be tenured and chaired at Harvard Business School, the first woman to teach in the school’s executive programs and the first to serve on a number of corporate boards.

Over the course of the conference, AMCP will offer over 30 programming selections including dedicated tracks on Medicare Part D and Specialty Pharmacy.

Boston is fabulous in the fall! Stick around for a Saturday hands-on experience on building and interpreting pharmacoeconomic models with Dan Malone, PhD, and Ed Armstrong, PharmD, professors at the University of Arizona College of Pharmacy titled *Advanced Issues in Pharmacoeconomic Modeling: Evaluating Uncertainty and Interpreting Cost-Effectiveness Data*.

Keep checking back on the AMCP website for updates, schedules and final programming — we’re putting together a compelling roster of speakers, programs and events designed to keep you on top of your game and at the forefront of your profession!
You won’t want to miss the Academy of Managed Care Pharmacy’s (AMCP’s) 2007 Educational Conference — the largest assembly of pharmacy and health care professionals dedicated solely to the issues of managed care pharmacy. This conference will highlight a myriad of activities, initiatives, breakthroughs and partnerships that are shaping the future of managed care pharmacy.

Join your colleagues in Boston for this premier educational and networking event!

Friday Afternoon Session —
Mark McClellan, MPA, MD, PhD

The Feature Presenter on Friday afternoon will be Dr. Mark McClellan, former Administrator for the Centers of Medicare & Medicaid Services.

Mark McClellan has had a highly distinguished tenure of public service. In the George W. Bush administration, he served as a member of the President’s Council of Economic Advisers and senior director for Health Care Policy at the White House (2001–2002), FDA commissioner (2002–2004), and CMS administrator from March 2004 until October, 2006.

Upon his retirement from government service, he joined the AEI-Brookings Joint Center for Regulatory Studies as a visiting senior fellow to work on developing and implementing ideas to drive improvements in high-quality, innovative, affordable health care. He is also an associate professor of Economics and associate professor of Medicine at Stanford University.

During the Clinton administration, Dr. McClellan was deputy assistant secretary of the Treasury for Economic Policy from 1998–1999, supervising economic analysis and policy development on a range of domestic policy issues. He subsequently directed Stanford’s Program on Health Outcomes Research and was a research associate of the National Bureau of Economic Research and a visiting scholar at the American Enterprise Institute. Additionally, he was associate editor of the Journal of Health Economics and co-principal investigator of the Health and Retirement Study (HRS), a longitudinal study of the health and economic well-being of older Americans.
Tuesday, October 23
8:00 am – 5:30 pm  FMCP Program: Learning Institute for Management of Chronic Kidney Disease
(by invitation only ... please visit www.fmcpnet.org)

Wednesday, October 24
8:00 am – 2:30 pm  FMCP Program continued from Tuesday: Learning Institute for Management of Chronic Kidney Disease
8:00 am – 5:30 pm  AMCP Committee Meetings
12:00 noon – 7:00 pm  Registration
1:00 pm – 5:00 pm  Pre-Conference Symposia
5:30 pm – 7:00 pm  Opening Night Reception

Thursday, October 25
6:00 am – 8:00 am  Breakfast Symposia
7:00 am – 5:00 pm  Registration
7:00 am – 5:00 pm  AMCP Committee Meetings
8:15 am – 9:15 am  Educational Sessions
8:30 am – 10:30 am  Workshop
9:00 am – 10:00 am  Leadership Luncheon (invitation only)
9:30 am – 10:30 am  Workshop
11:30 am – 1:00 pm  Leadership Luncheon (invitation only)
1:30 pm – 2:30 pm  Opening General Session
2:45 pm – 5:30 pm  Educational Sessions

Friday, October 26
6:00 am – 8:00 am  Breakfast Symposia
7:00 am – 5:00 pm  Registration
8:30 am – 10:30 am  Educational Sessions
9:00 am – 11:00 am  Round Table Discussions
9:45 am – 10:45 am  Educational Sessions
11:00 am – 12:30 pm  General Session
12:30 pm – 2:45 pm  Managed Care Industry Forum
2:45 pm – 6:00 pm  Managed Care Pharmacy Residency Showcase
2:45 pm – 3:45 pm  Educational Sessions
4:00 pm – 5:00 pm  Educational Sessions
5:00 pm – 6:00 pm  Student and New Member Reception

Saturday, October 27
8:00 am – 10:30 am  Registration
8:30 am – 10:30 am  Workshop
10:30 am  Adjourn
**Registration Form**

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Full registration fees must accompany this form for registration to be processed. Confirmations will be sent to all confirmed participants. If an e-mail address is provided, confirmations will be sent via e-mail. Questions? Call Experient at (847) 940-2107.

**ATTENDEE INFORMATION [required]**

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<td>First Name</td>
<td></td>
</tr>
<tr>
<td>Last Name</td>
<td></td>
</tr>
<tr>
<td>MY AMCP MEMBERSHIP NUMBER [IF APPLICABLE]</td>
<td></td>
</tr>
<tr>
<td>Title</td>
<td></td>
</tr>
<tr>
<td>Company</td>
<td></td>
</tr>
<tr>
<td>Address 1</td>
<td></td>
</tr>
<tr>
<td>Address 2</td>
<td></td>
</tr>
<tr>
<td>City</td>
<td></td>
</tr>
<tr>
<td>State</td>
<td></td>
</tr>
<tr>
<td>Zip Code</td>
<td></td>
</tr>
<tr>
<td>Registrant’s Telephone</td>
<td></td>
</tr>
<tr>
<td>Fax</td>
<td></td>
</tr>
<tr>
<td>Registrant’s E-Mail Address</td>
<td></td>
</tr>
<tr>
<td>Administrative Assistant’s E-mail Address [Optional]</td>
<td></td>
</tr>
<tr>
<td>Emergency Contact and Telephone Number</td>
<td></td>
</tr>
</tbody>
</table>

**REGISTRATION FEES/CATEGORIES [please check the appropriate circle below]**

<table>
<thead>
<tr>
<th>Category</th>
<th>On-Site (received after 9/24/07)</th>
<th>Pre-Registration (received on or before 9/24/07)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Health Care Practitioner Member (physicians/nurses)</td>
<td>$295</td>
<td>$295</td>
</tr>
<tr>
<td>Pharmacist Member (licensed pharmacists)</td>
<td>$295</td>
<td>$295</td>
</tr>
<tr>
<td>Associate Member (non-pharmacists/physicians/nurses)</td>
<td>$390</td>
<td>$390</td>
</tr>
<tr>
<td>Government Employee (AMCP member)</td>
<td>$300</td>
<td>$300</td>
</tr>
<tr>
<td>Government Employee (non-member pharmacists/physicians/nurses)**</td>
<td>$540</td>
<td>$540</td>
</tr>
<tr>
<td>Government Employee (non-member non-pharmacists/physicians/nurses)**</td>
<td>$740</td>
<td>$740</td>
</tr>
<tr>
<td>Non-Member</td>
<td>$840</td>
<td>$840</td>
</tr>
<tr>
<td>Student Member</td>
<td>$80</td>
<td>$80</td>
</tr>
<tr>
<td>Resident/Fellow/Graduate Member</td>
<td>$80</td>
<td>$80</td>
</tr>
<tr>
<td>Student Non-Member</td>
<td>$60</td>
<td>$60</td>
</tr>
<tr>
<td>Press</td>
<td>$60</td>
<td>$60</td>
</tr>
</tbody>
</table>

*If registering for one day, please indicate which day you will be attending:  
Wednesday  
Thursday  
Friday  
Saturday

**DEMOGRAPHIC INFORMATION [required]**

**METHOD OF PAYMENT**

- Check made payable to Experient/AMCP for $_________ (in U.S. funds drawn on a U.S. bank)
- Charge $_________ to my credit card (credit card will be charged immediately)
- Visa  
- MasterCard  
- American Express  
- Discover

<table>
<thead>
<tr>
<th>Field</th>
<th>Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Card Number</td>
<td></td>
</tr>
<tr>
<td>Expiration Date (Month/Year)</td>
<td></td>
</tr>
<tr>
<td>Cardholder Printed Name (as it appears on your card)</td>
<td></td>
</tr>
<tr>
<td>Cardholder Signature</td>
<td></td>
</tr>
</tbody>
</table>

**Want to Register**

- Online: www.amcp.org  
- By fax: 800 521 6017  
- Mail: Experient/AMCP • 108 Wilmot Road, Suite 400 • Deerfield, IL 60015-5124

Cancellation of participant registration must be requested in writing and must be received by Wednesday, September 26, 2007. A $150 administrative fee will be assessed on all cancellations. No cancellation/refund requests will be granted after Wednesday, September 26, 2007. Registrant substitutions will be accepted with written notification from the original registrant. An administrative fee of $30 (other fees may apply) will be assessed. Only one substitution per registrant is allowed. No registration transfers to other AMCP national meetings. Note: A valid photo ID must be presented during registration check-in to obtain your badge and meeting materials.
ATTENDEE INFORMATION [required]

FIRST NAME LAST NAME
TITLE
COMPANY
ADDRESS 1
ADDRESS 2
CITY STATE ZIP CODE
REGISTRANT'S TELEPHONE FAX
REGISTRANT'S E-MAIL ADDRESS
ADMINISTRATIVE ASSISTANT'S EMAIL ADDRESS (OPTIONAL)
SHARING ROOM WITH (INCLUDE AGES IF UNDER 19)

HOTEL INFORMATION

Marriott Copley Place
Rates: $249 single occupancy / $257 double occupancy
Westin Copley Place
Rates: $249 single/double occupancy
Hilton Back Bay
Rates: $249 single/double occupancy

Arrival Date: October _______, 2007
Departure Date: October _______, 2007
Occupancy of Room: [please check one] ☐ Single ☐ Double
ADA Requests: [please check all that apply] ☐ Mobile ☐ Audio ☐ Visual
Special Requests: [Based on availability. Special requests will be made on your behalf, but cannot be guaranteed. Non-smoking room, double/double beds, cribs, etc.]

METHOD OF PAYMENT [All reservations require a $249 room deposit plus registration fee.]

☐ Check deposit made payable to Experient/AMCP for $ ____________ (in U.S. funds drawn on a U.S. bank)
☐ Charge my credit card — ☐ Visa ☐ MasterCard ☐ American Express ☐ Discover

CARD NUMBER EXPIRATION DATE (MONTH/YEAR)
CARDHOLDER PRINTED NAME (AS IT APPEARS ON YOUR CARD)
CARDHOLDER SIGNATURE

INTERNET • Make your hotel reservations online through the AMCP website at www.amcp.org. A credit card deposit is required to confirm your hotel reservation. See ‘Method of Payment’ below

FAX • When payment is by credit card, you may complete this form and fax it to Experient. All arrangements will be confirmed in writing. The fax number is: 800 521 6017. A $249 credit card room deposit is required to confirm your hotel reservation. Please note that your credit card will be charged when this form is submitted.

MAIL • Simply complete this form and return it to Experient with a $249 deposit, or credit card to be charged. See ‘Method of Payment’ below. Please note that your credit card will be charged when this form is submitted to confirm your room reservation. All arrangements will be confirmed in writing. If an email address is provided, confirmations will be sent via email.

Experient/AMCP
108 Wilmot Road, Suite 400
Deerfield, IL 60015-5124

IMPORTANT HOUSING NOTES •

• You must be a confirmed registrant to obtain housing under AMCP’s block.
• All reservations require a $249 room deposit. Please note that your credit card will be charged when this form is submitted to confirm your room reservation.
• In the event that you decide to depart earlier than confirmed at the time you check-in, you will be charged a $50 early departure fee by the hotel.
• All new reservations should be made directly with Experient by 5:00 pm CDT Monday, September 24, 2007. After September 24, you may continue to contact Experient for reservation changes, cancel requests or new reservations (based on availability) until 5:00 pm CDT Wednesday, October 3, 2007. You can begin contacting hotels directly for all reservation needs starting Friday, October 12, 2007. Room cancellations must occur 14 business days prior to your arrival. Failure to cancel within the appropriate time frame will result in forfeiture of your entire $249 room deposit.
• When cancelling a reservation by telephone with the hotel, record the date, cancellation number, and the name of the person accepting the cancellation.

Ways to Make Hotel Accommodations

• Online: www.amcp.org
• By fax: 800 521 6017
• By mail: Experient/AMCP
108 Wilmot Road, Suite 400
Deerfield, IL 60015-5124
Perhaps you have wondered if an organization exists to represent all the special facets of your professional life. One does.

The Academy of Managed Care Pharmacy (AMCP) is a professional association of pharmacists and other health care professionals and associates whose members serve their patients and the public based on the principles of managed care. Though AMCP members come from a variety of increasingly diverse backgrounds, they all share an overriding, common goal — to ensure positive health care outcomes and improved quality of life through appropriate and accessible medication therapy.

Vision and Mission

Vision — Improved quality of life through appropriate and accessible medication therapy.

Mission — AMCP’s mission is to empower its members to serve society by using sound medication management principles and strategies to achieve positive patient outcomes.

Something different. Something more. Explore your opportunities with AMCP.

AMCP is intimately familiar with the unique position of health care professionals in managed care pharmacy environments. That means we can provide support, professional growth and career opportunities unsurpassed by any other organization. No matter where you are employed — managed care organization, hospital, clinic, community pharmacy, pharmaceutical manufacturer, academic or research institution — you’re a welcome member of AMCP.

Is it true that what you get out of a professional organization corresponds with your level of involvement?

Of course it is. However, we believe the greatest rewards come from associating with those who offer the most potential to begin with. That’s why AMCP membership continues to grow. Our network of health care professionals can help you lead your organization in directions that may have never been considered. At the same time, your ability to make a difference in patient care delivery grows many times over.

Your opportunities with AMCP include:

- **Networking** with colleagues and other health care professionals.
- **Sharing** ideas and exchanging information.

**Secure your future with AMCP guidance.**

The world of pharmacy is changing rapidly. Initiatives underway in both the public and the private sectors are embracing the principles of managed care pharmacy, and pushing the limits of the discipline further into medical practice than they have ever been before. AMCP programs and resources are a large part of that cutting edge, and AMCP members are acknowledged experts in the field.

AMCP keeps you on top of changes in the health care arena and provides you with the information you need to make wise practice and career choices. Through AMCP membership, you can become an active participant — a leader — who will help direct the course of managed care in the coming years. You can get involved with committees and contribute to numerous publications and educational programs as part of your membership.

**Membership categories and benefits.**

AMCP’s continuous growth is the result of a vital and expanding list of services. Our core constituency is **Pharmacist** members. This membership confers full voting rights and the privilege to serve on all AMCP committees. Pharmacist members are also eligible to run for the Board of Directors. **Health Care Practitioner (Non-Pharmacist)** is our newest membership category, which includes doctors and registered nurses who have a direct involvement in the practice of managed care pharmacy. Health Care Practitioner (Non-Pharmacist) members may serve on all AMCP operating committees. Dues are the same as Pharmacist member dues. **Associate** members are all other individuals who are interested in the advancement and development of managed care pharmacy practices, regardless of practice environment. **Student** members must be enrolled in a program of studies at an accredited college of pharmacy. **Resident/Fellow/Graduate** members must be enrolled in a full-time recognized postgraduate program.

Visit AMCP’s website at [www.amcp.org](http://www.amcp.org) to join today!
PLEASE ENTER THE AMCP MEMBER WHO REFERRED YOU FOR MEMBERSHIP (IF APPLICABLE).

REFERRED BY

PLEASE PRINT OR TYPE.

MEMBER INFORMATION

☐ Mr. ☐ Ms. ☐ Mrs. ☐ Dr.

FIRST NAME ___________________________ LAST NAME ___________________________

TITLE ___________________________

ORGANIZATION NAME ___________________________

ORGANIZATION ADDRESS ___________________________

CITY ___________________________ STATE ______ ZIP CODE ______

HOME ADDRESS ___________________________

CITY ___________________________ STATE ______ ZIP CODE ______

SEND ALL MAILINGS TO MY: ☐ Company Address ☐ Home Address

WORK TELEPHONE ___________________________ FAX ___________________________

HOME TELEPHONE ___________________________ CELLULAR TELEPHONE ___________________________

EMAIL ADDRESS (PRIMARY) ___________________________

EMAIL ADDRESS (SECONDARY) ___________________________

ANNUAL MEMBERSHIP RATES INFORMATION

☐ Pharmacist Member ___________________________ $240 per year

☐ Health Care Practitioner (Non-Pharmacist) Member ___________________________ $240 per year

☐ Associate Member ___________________________ $440 per year

☐ Student Member ___________________________ $35 per year

☐ Resident/Fellow/Graduate Member ___________________________ $85 per year

METHOD OF PAYMENT

☐ Check made payable to AMCP for $ _________ (in US funds drawn on a US bank)

☐ Charge $ _________ to my credit card: ☐ Visa ☐ MasterCard ☐ American Express

CARD NUMBER ___________________________ EXPIRATION DATE ___________________________

CARDHOLDER SIGNATURE ___________________________ CARDHOLDER PRINTED NAME ___________________________

II. Which of the following best describes your employer? (check one)

☐ Association ☐ Medical Education

☐ Claims Processor ☐ Med/Physician Group

☐ College/University ☐ Not Employed/Retired

☐ Community Service Provider ☐ PBM/PBM Mail Service

☐ Consulting Firm ☐ Pharm Management/

☐ Government/Military ☐ PSAO

☐ HMO/PO/Health Plan/IHS ☐ Pharmaceutical Manufacturer

☐ Home Care ☐ Press

☐ Hospital ☐ Retail Pharmacy

☐ Information Management ☐ Spec Pharmacy

☐ Legal/Advertising/ ☐ Wholesale/ Professional Services

☐ Long-term Care ☐ Distribution/GPO

☐ Mail Service Only ☐

☐ Other (specify) ___________________________

III. Which of the following best describes your job function(s)? (check one)

☐ Asst Pharm Director/ ☐ Not Employed/Retired

☐ Senior Pharm Management ☐ Nurse

☐ Clinical Coord/Operations ☐ Outcomes Research/

☐ Contracting/Purchasing ☐ Clinical Science

☐ Consultant ☐ Pharm Director

☐ Customer Service ☐ Pharm Manager

☐ Distrib/supply Chain ☐ Physician

☐ Editorial ☐ President/CEO

☐ Financial Management ☐ Prof/Trade Relations

☐ Formulary Management ☐ School/College Faculty

☐ Legal/Govt Affairs ☐ Staff/Clinical

☐ Medical Affairs ☐ Pharmacist

☐ Medical Director/CMO ☐ Student/Resident/ Fellow

☐ Med-Pharm Information Management/education ☐ Senior Management/ VP/COO

☐ Network Management ☐

☐ Other (specify) ___________________________

IV. How many years have you been in your current role?

_________________ year(s)

DEMOGRAPHIC INFORMATION

PLEASE TELL US:

I. What degrees/designations do you hold?

☐ B.S. Pharmacy ☐ Pharm.D.

☐ M.P.A. ☐ M.P.H.

☐ Ph.D. ☐ J.D.

☐ M.B.A. ☐ R.Ph.

☐ M.D. ☐ R.N.

☐ Other (specify) ☐ D.O.