HIV/HEPATITIS ISSUE

The Effect of Hepatitis C Treatment Response on Medical Costs: A Longitudinal Analysis in an Integrated Care Setting

Antiviral Regimen Complexity Index as an Independent Predictor of Sustained Virologic Response in Patients with Chronic Hepatitis C

A Qualitative Study Examining HIV Antiretroviral Adherence Counseling and Support in Community Pharmacies

BENEFIT MANAGEMENT

Medical Costs Associated with Use of Systemic Therapy in Adults with Colorectal Cancer

Identifying Patient Characteristics Associated with High Schizophrenia-Related Direct Medical Costs in Community-Dwelling Patients

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A symposium held at the American Society of Health System Pharmacists (ASHP) Clinical Mid-Year in Dallas, Texas, helped Norrie Thomas see clearly that pharmacy directors would have to play a more significant role in the business of managed care in the future—and that pharmacists would have to take the lead to make it happen.

“Several of us in pharmacy benefit management firms (PBMs) and other managed care pharmacy positions realized that the pharmacy director was not just a staff function,” Thomas says. “We saw an entrepreneurial trajectory for pharmacists in this new world. But it was just as clear that many pharmacists were not on that same path and didn’t share that vision of the appropriate role for pharmacy directors.”

That realization led Thomas to join Perry Cohen, Robert Navarro, Pete Pena, Jay Messeroff, Al Carver, John Cuifo, and Hank Blissenbach in establishing a new group to support pharmacists with the same passion for combining clinical management with business in a new career path in managed care: the Academy of Managed Care Pharmacy (AMCP).

Thomas has ventured well down the entrepreneurial path in her career. In 1990, she helped found Clinical Pharmacy Advantage (CPA), a company devoted to building a national system of managed care that coordinated the multiple decision makers—physicians, pharmacists, payers, patients, and pharmaceutical manufacturers—in an effort to improve patient care through better use of pharmaceuticals. As the President and Chief Operating Officer, Thomas expanded this start-up company into a major PBM firm that successfully won business from more established companies in a competitive environment.

Under Thomas’s leadership, CPA grew from no members in August 1990 to more than 7,000,000 members in April 1993, shortly before it was purchased by McKesson Corporation/PCS. CPA’s clinical expertise was rolled into the Pharmaceutical Care Services (PCS) book of business within the McKesson firm. Within 18 months of the purchase, the company delivered clinical services to 38 million lives and more than 1,000 customers and significantly contributed to the financial performance of McKesson Corporation. The operations to deliver these clinical services grew from 8 employees in 1990 to more than 150 employees by January 1994.

When the cover photo was taken in 1995, Thomas had joined Eli Lilly & Co. as Executive Director for Europe, the Middle East and Africa and was working in London. At this juncture in managed care history, Thomas recalls, there was “a lot of excitement surrounding the purchase of PBMs by major pharmaceutical firms.” Merck bought Medco; SmithKlineBeecham purchased Diversified Pharmaceutical Services; and Eli Lilly took over PCS.

“PBMs were so valuable at that time,” Thomas says. “But, many of us had doubts about whether having drug manufacturers own and operate PBMs would work.” Those doubts, she notes, were justified. Today, pharmacy companies and PBMs partner together but not in the same organizational structure of the 1990s.

Thomas has served AMCP on many committees, calling her “most memorable assignment” that of her role as Interim Executive Director of the AMCP Foundation from August 2010 to June 2012. Prior to her role at the Foundation, she was equally honored when she received AMCP’s highest recognition, the Steven G. Avey Award, at the San Diego meeting in 2010.

Still on her entrepreneurial path, Thomas today is President and founder of the Manchester Square Group, a pharmacy consulting company that focuses on designing and testing new business initiatives in health care, strategic planning, and market assessment, with an emphasis on pharmaceutical innovation and PBM services. She also is a Senior Fellow for the Center for Leading Healthcare Change at her alma mater, the University of Minnesota, where she obtained her bachelor’s and master’s degrees in pharmacy and her PhD in Pharmacy Administration. The university recently honored Thomas as an Outstanding Alumna.

She is also a published author of several books, including her most recent, An Unbalanced Success: Life. Leadership. Libretto, which is a study of the qualities that distinguish outstanding leaders.

As her own career has progressed, Thomas has watched and participated as the practice of managed care pharmacy has taken a varied course in the years since AMCP was founded. “The PBM industry has matured. We need teams of experts from all areas of health care to work together to tackle the many challenges facing pharmacy benefit management. AMCP is taking the lead again by opening our membership to these teams of professionals, while continuing to strengthen our core: pharmacy managed care. We’ve all recognized that to be successful, we and our field have to be willing to make significant changes.”
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*Journal of Managed Care Pharmacy* (ISSN 1944-706X) is published 9 times per year and is the official publication of the Academy of Managed Care Pharmacy (AMCP), 100 North Pitt St., Suite 400, Alexandria, VA 22314; 703.683.8416; 800.TAP.AMCP, 703.683.8417 (fax). The paper used by the *Journal of Managed Care Pharmacy* meets the requirements of ANSI/NISO Z39.48-1992 (Permanence of Paper) effective with Volume 7, Issue 5, 2001; prior to that issue, all paper was acid-free. Annual membership dues for AMCP include $90 allocated for the *Journal of Managed Care Pharmacy*. Send address changes to JMCP, 100 North Pitt St., Suite 400, Alexandria, VA 22314.
The Effect of Hepatitis C Treatment Response on Medical Costs: A Longitudinal Analysis in an Integrated Care Setting

M. Michele Manos, PhD, MPH, DVM; Jeanne Darbinian, MPH; Jaime Rubin, MPH; G. Thomas Ray, MBA; Valentina Shvachko, MS; Baris Deniz, MSc; Fulton Velez, MD, MSPharm, MBA; and Charles Quesenberry, PhD

ABSTRACT

BACKGROUND: Studies suggest that chronic hepatitis C patients who achieve sustained virologic response (SVR) have lower risks of liver-related morbidity and mortality. Given the substantial costs and complexity of hepatitis C virus (HCV) antiviral treatment, post-treatment benefits are important to understand.

OBJECTIVE: To determine whether health care costs and utilization for up to 5 years after treatment differed between patients who achieved SVR and those who did not.

METHODS: Kaiser Permanente Medical Care Program patients receiving HCV treatment with pegylated interferon and ribavirin (Peg-IFN/RBV) from 2002 to 2007 were retrospectively analyzed, excluding those with human immunodeficiency virus (HIV) or chronic hepatitis B. Health care utilization and costs for up to 5 years after treatment completion were derived from electronic records. We compared mean annual cost and overall post-treatment costs (standardized to year-2007 dollars), and yearly utilization counts between the SVR and non-SVR groups, adjusting for pretreatment costs, age, sex, baseline cirrhosis, and race using gamma and Poisson regression models.

RESULTS: The 1,924 patients eligible for inclusion were a mean age of 50 years; 63% male; 58% white, non-Hispanic; 62% with genotype 1; and 48% who had achieved SVR. The mean duration of post-treatment time was 3 years, and patients without SVR incurred significantly higher health care costs than patients with SVR. For each post-treatment year, total adjusted costs were significantly higher in the non-SVR group than in the SVR group, particularly for liver-related tests, outpatient drugs, and hospitalizations, were significantly lower than did those with SVR. Our observations are consistent with the potentially lower risk of severe liver disease among patients with SVR.

What is already known about this subject

• Chronic hepatitis C virus (HCV) is the most common blood-borne infection in the United States, affecting approximately 4 million people, most of whom do not know they are infected. Related disease progresses slowly over several decades, and symptoms often go unnoticed until patients develop advanced liver disease, such as decompensated cirrhosis and hepatocellular carcinoma.

• The costs of treating HCV-related complications are expected to rise substantially in the next 5 to 10 years, as the majority of patients will have been infected for more than 2 decades and are at increased risk of developing advanced liver disease.

• Achieving sustained virologic response (SVR) is the primary goal of HCV treatment, and studies suggest that it potentially reduces the risk of advanced liver disease, liver transplant, and liver-related death over the long term. The impact of SVR on resource use and health care costs in the short term has not been fully characterized.

What this study adds

• We conducted a retrospective study of patients receiving treatment with pegylated interferon and ribavirin in the Kaiser Permanente Medical Care Program of Northern California from 2002 to 2007 to quantify the short-term cost and utilization impact of achieving SVR. Using electronic medical records, health care utilization and costs were assessed for up to 5 years after treatment ended. Post-treatment all-cause costs per person per year were $6,301 and $10,149 for the SVR and non-SVR groups, respectively. The adjusted difference in yearly total mean costs was $2,648 (95% CI, 737-4,560).

• When considering costs by post-treatment year, total adjusted costs were significantly higher (up to 1.7 times) in the non-SVR group than in the SVR group, driven mostly by hospital and outpatient pharmacy costs. When all post-treatment years were considered collectively, the non-SVR group had significantly higher costs overall (RR = 1.41; 95% CI, 1.17-1.69) and in each category of costs. The adjusted difference in yearly total mean costs was $2,648 (95% CI, 737-4,560).

• During post-treatment years 1-5, adjusted yearly liver-related hospitalization rates were up to 2.45 times higher (95% CI, 1.56-3.85), and medicine/GI clinic visit rates were up to 1.39 times higher (95% CI, 1.23-1.54) in the non-SVR group compared with the SVR group.

CONCLUSION: Health care utilization and costs after HCV antiviral therapy with Peg-IFN/RBV, particularly for liver-related tests, outpatient drugs, and hospitalizations, were significantly lower for patients who achieved SVR than for those without SVR. Our observations are consistent with the potentially lower risk of severe liver disease among patients with SVR.


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A pproximately 4 million people in the United States are chronically infected with hepatitis C virus (HCV).1-3 Hepatitis C is a slowly progressing disease that is relatively asymptomatic until severe liver disease develops, and at least 50% of the infected population remains undiagnosed in the United States today.4,5 Despite the often asymptomatic early stages of the condition, chronic hepatitis C can result in liver failure, including decompensated cirrhosis (DCC) or hepatocellular carcinoma (HCC).4,6,7

A substantial portion of both the economic and health burden of HCV is driven by the development of advanced liver disease (i.e., DCC or HCC).4 Currently, hepatitis C is the leading cause of HCC and liver transplants in the United States, and studies estimate that liver cirrhosis and HCC will increase 30.5% and 50%, respectively, in the next decade.8-10 Likewise, the health care costs related to HCV were estimated to be $5.46 billion in 1997 and are predicted to increase to $10.7 billion over the next decade.11,12 Recently published HCV economic analyses estimated that annual total cost per patient was $20,961 for patients with HCV compared with $5,451 in a matched uninfected cohort.13

The primary goal of HCV treatment is to prevent morbidity and mortality associated with resultant chronic liver disease. The desired outcome of treatment is sustained virologic response (SVR), defined as undetectable HCV in plasma at least 6 months after the completion of anti-HCV therapy.14 Based on clinical and laboratory observations, SVR is considered as defining virologic cure.15,16 Until the spring of 2011, the standard of care for all genotypes of HCV was the combination of pegylated interferon and ribavirin (Peg-IFN/RBV), which leads to SVR in approximately 40% of patients with genotype 1 and 70% to 80% of patients with genotype 2 or 3.14 Recent studies have shown that SVR is associated with a >80% reduction in complications such as HCC, end-stage liver disease, liver transplant, liver-related death, diabetes, as well as overall mortality.17,23

Previous studies that have assessed the economic and clinical value of successful HCV treatment extrapolate the positive impact of SVR on future complications.24-28 In these studies, an assumption was that virologic cure would provide long-term (i.e., over the course of a person’s lifetime) economic and clinical value by reducing future risks of disease-related complications. However, few studies have looked at more immediate long-term cost benefits of SVR. We sought to investigate whether patients who achieved SVR had reduced health care costs compared with those who did not achieve SVR during the period 1 to 5 years after treatment. Specifically, in an integrated managed care setting, we compared the direct medical-care costs and total health care resource utilization up to 5 years following HCV treatment with Peg-IFN/RBV among patients who achieved SVR versus those whose treatment was not successful.

### Methods

#### Setting and Base Population

We studied patients who had undergone HCV treatment within the Northern California Kaiser Permanente Medical Care Program (KPNC). The comprehensive, integrated health care delivery system serves more than 3.2 million members in the San Francisco and Sacramento Greater Metropolitan areas. The membership is representative of the area’s total insured population except for persons with extremes in income.29,30 Comprehensive, electronic administrative and clinical data for all KPNC patients with hepatitis C are maintained in the Viral Hepatitis Registry (VHR) and at the time of this investigation included records dated from 1995 through 2008 for 40,307 historical and current patients with hepatitis C. The study protocol was approved by the Institutional Review Board of the Kaiser Foundation Research Institute.

#### Study Populations

We identified 3,250 adult patients who had undergone a course of at least 4 weeks of Peg-IFN/RBV antiviral therapy for chronic HCV infection between January 1, 2002, and December 31, 2007. We did not include treatment courses defined as pre-transplant (treatment initiation within 18 months prior to a transplant date identified by the KP Transplant Registry database) or treatments occurring after liver transplant. We required at least 11 months of membership in the KPNC health plan for the 1 year prior to treatment initiation and the 1 year after the end of treatment. The end of treatment was defined by the last prescription dispense date plus days of supply. We excluded patients with chronic viral hepatitis B (HBV) and/or human immunodeficiency virus (HIV) co-infection (based on their inclusion in KPNC disease registries), a record of enrollment in an HCV clinical trial, any prior treatment for HCV within the past 12 months, unknown sustained viral response (SVR) status, and HCV genotype unknown or other than 1, 2, or 3. Figure 1 delineates the process. If more than 1 eligible HCV treatment course occurred for a patient during the study period (greater than 12 months apart), we selected the most recent.

For each patient, post-treatment follow-up continued for 1, 2, 3, 4, or 5 years (12-month periods) after the date of ending HCV treatment. Years of eligible follow-up were determined by death, disenrollment from the health plan, or December 31, 2008, whichever occurred first. Inclusion required health plan membership for 11 of the 12 months of that individual’s year of follow-up, or death with at least 1 month of membership in that year. For example, an otherwise eligible patient whose treatment ended in December 2007 could contribute only 1 year of follow-up, and a patient whose treatment ended in June of 2006 could contribute only 2 years (the third potential year of follow-up being truncated in December 2008 and being ineligible). A detailed flow diagram of post-treatment attrition of the cohort is shown in Figure 1.
The Effect of Hepatitis C Treatment Response on Medical Costs: A Longitudinal Analysis in an Integrated Care Setting

**FIGURE 1 Assembly and Attrition of Study Cohort**

Adult health plan members with ≥4 week eligible course of pegylated interferon and ribavirin HCV therapy during years 2002-2007.

**EXCLUDED**:  
- 855 (26%) lacking ≥11 months of membership 1 year prior to and/or 1 year after therapy, and/or continuous membership during therapy  
- 37 (1%) with hepatitis B virus co-infection  
- 64 (2%) with HIV co-infection  
- 6 (<1%) with HCV clinical trial participation  
- 103 (3%) not HCV genotype 1, 2, or 3 (68 unknown, 35 other)  
- 217 (6%) with unknown treatment response (SVR status)  
- 44 (1%) treated within 1 year prior to eligible treatment course

- Censored December 31, 2008 (n=279)  
- Health plan disenrollment (n=144)  
- Deceased (n=13)

436 (23%)  

- Censored December 31, 2008 (n=285)  
- Health plan disenrollment (n=80)  
- Deceased (n=13)

378 (20%)  

- Censored December 31, 2008 (n=301)  
- Health plan disenrollment (n=53)  
- Deceased (n=10)

364 (19%)  

- Censored December 31, 2008 (n=294)  
- Health plan disenrollment (n=22)  
- Deceased (n=5)

321 (17%)  

- n=3,250*  
- n=1,924  
- n=1,488  
- n=1,110  
- n=746  
- n=425d

*Identified from 40,307 hepatitis C patients in the KPNC Viral Hepatitis Registry.  
*Does not include treatment courses initiated after or within 18 months prior to liver transplant.  
*Exclusions conducted hierarchically.  
*During the Year 5 period, 8 additional deaths occurred.  
HCV=hepatitis C virus; HIV=human immunodeficiency virus; KPNC=Northern California Kaiser Permanente Medical Care Program; SVR=sustained virologic response.

For patients who died in a follow-up year, utilization and costs up to the time of death were included for that year. This method is based, in part, on the assumption that the patient would have remained a health plan member for the entire year had they not died. We did not adjust cost estimates for time spent alive within that final follow-up year. We chose this approach, to better capture the health care events occurring prior to death, rather than excluding patients from their death year and potentially missing these major costs.

**Data Collection**

Utilization and cost data were obtained for the period 1 year prior to treatment, during treatment, and all eligible years post-treatment for each patient. Costs for services provided by KPNC were obtained from the Cost Management Information System, an automated system that integrates use and financial databases. Thus, the payer perspective was adopted for the study. Costs, including program and facility overhead, are generated for services using standard accounting methods and program-specific relative value units. From these, we obtained costs of hospitalization and outpatient encounters, including emergency department and office visits as well as radiology and laboratory services. We obtained outpatient pharmacy costs from KPNC’s Pharmacy Information Management System, which records information on all prescription drugs dispensed at KPNC outpatient pharmacies. For services covered by KPNC but provided by non-KPNC vendors, we used payments made to those vendors. This study does not include any patient out-of-pocket expenses, and all costs were adjusted to year-2007 dollars using the Consumer Price Index.
We obtained health care utilization data from the KPNC electronic medical record system and other automated databases. These databases capture laboratory tests and results, hospitalizations, emergency department visits, and outpatient clinic visits. Laboratory tests were stratified by whether they were considered liver-disease related (codes for all HCV tests, creatinine, bilirubin, serum albumin, alanine amino transferase, aspartate amino transferase, gamma-glutamyl transferase, alpha-fetoprotein). Diabetes was assigned by whether the patient was included in the KPNC Diabetes Registry. Cirrhosis was defined by evidence on a liver biopsy or a medical record diagnosis (equivalent to International Classification of Diseases, Ninth Edition, Clinical Modification (ICD-9-CM) codes 571.2, 571.5, 571.6).

Baseline, on-treatment, and response information was obtained from the KPNC VHR databases. SVR status was assigned based on laboratory records and defined as is standard: undetectable viral RNA (lower limit of detection, 7 IU/ml) at 24 weeks or later after the course of treatment.

Different HCV genotypes require distinct antiviral therapy regimens and were grouped to reflect this. Selected findings are presented stratified by the viral genotype groups, making them available for future studies that may consider on-treatment costs or utilization in combination with post-treatment information.

**Analyses of Differences in Mean Medical Costs**

We obtained estimates of adjusted differences in mean annual post-treatment costs between the non-SVR group and those who attained SVR, using linear regression models in which the dependent variable was cost. We assessed total costs and costs stratified by care setting, including hospital, outpatient pharmacy, and outpatient nonpharmacy. “Hospital costs” included the cost of hospitalizations (including same-day hospitalizations), skilled nursing facility stays, home health care visits, and hospice care. Outpatient nonpharmacy costs included the cost of laboratory and radiology services, emergency department visits, clinic visits, and durable medical equipment.

The primary independent variable was SVR group (comparing those who did not achieve SVR with those who did). We adjusted for age at the end of treatment, race/ethnicity, sex, and history of cirrhosis (prior to start of treatment). We also included total costs incurred during the 1-year period prior to treatment initiation (entered as quintiles) as a proxy for baseline health status and propensity to use services. Utility of this proxy was evidenced by the observation that inclusion of it in models ameliorated the substantial effects of pretreatment diabetes or depression. We applied weighting based on total number of post-treatment years in the study and obtained estimates for the entire analytic cohort and for each HCV genotype subset (1 and 2/3).

**Analyses of Proportional Differences in Mean Medical Costs**

To estimate the proportional differences in post-treatment costs (expressed as rate ratios [RRs]) showing the ratio of the non-SVR group compared with the referent SVR group, we ran separate generalized models under the gamma distribution with log link (i.e., log-linear) for each year of follow-up. For these log-linear gamma models, the dependent variable was the person’s direct medical cost in that year and the primary independent variable was SVR group (comparing those who did not achieve SVR with those who did). Because gamma distribution modeling would exclude any records with no costs, we added $1 to each care category of summarized costs in each post-treatment year that an individual cohort member remained in the study. This allowed us to retain all eligible records under study (for a given year and care setting of cost). We adjusted for age at the end of treatment, race/ethnicity, sex, history of cirrhosis, and pretreatment costs.

In addition to modeling costs separately for each post-treatment year, we also used log-linear gamma models in which we combined post-treatment costs for all years of follow-up in a series of repeated measures models with estimation via generalized estimating equations (GEE) with an autoregressive covariance structure to account for correlation among different post-treatment years for the same person. We ran these models for the entire cohort and also stratified by HCV genotype (1 versus 2/3). Furthermore, we tested for heterogeneity in the SVR effect over time by including all years for the cohort in a repeated measures model (via GEE) that contained an interaction term of post-treatment year by SVR–non-SVR indicator.

**Analyses of Health Services Utilization**

To assess differences in health care services use by SVR group, we used Poisson regression, with allowance for over-dispersion (variance > mean) or under-dispersion (variance < mean). The dependent variable was counts of health care services use for each care category assessed (e.g., hospitalizations, outpatient laboratory test results, ambulatory care clinic visits). Liver-related laboratory tests included liver chemistry and any HCV tests. For hospitalizations, we counted admissions that included an overnight stay. The principal predictor was SVR group, adjusting for age at end of treatment, sex, race/ethnicity, history of cirrhosis prior to start of treatment, and quintile of pretreatment costs. As with the cost analysis, we ran separate models for each post-treatment year. We also tested for heterogeneity in the SVR effect over time by including all years in a repeated measures model that contained an interaction term of post-treatment year by SVR status. We used a GEE approach to account for the within-patient correlation in yearly utilization counts.
Results

Characteristics of the Analytic Cohort

The complete analytic cohort consisted of 1,924 patients of whom 63% were male, 58% non-Hispanic white, and 62% had HCV genotype 1. Almost half (48%) had achieved SVR. The mean age at the end of treatment was approximately 50 years; and mean post-treatment (follow-up) time was 3.0 and 2.9 years in the SVR and non-SVR groups, respectively. Table 1 shows characteristics of the total cohort stratified by treatment response group. Numbers of patients eligible for inclusion in analyses decreased by the year of follow-up (Figure 1); in year 5, only 425 patients remained in the study population. Cohort characteristics such as demographics and SVR status were virtually identical in all post-treatment years (not shown).

Post-Treatment Activity

Post-treatment total (all cause) costs per person per year were an average of $8,286 for the entire cohort, and $6,301 and $10,149 for the SVR and non-SVR groups, respectively (Table 2). Compared with those who attained SVR, patients in the non-SVR group incurred higher post-treatment costs in all categories assessed (total, hospital, and outpatient, whether pooled or distinguished as nonpharmacy and pharmacy). During each of the post-treatment years, 85% to 87% of the SVR group had no hospitalizations compared with 73% to 82% of the non-SVR group each year (data not shown).

Table 2 also shows that post-treatment utilization per person-year was higher in the non-SVR compared with the SVR group for the 4 major categories of services studied: hospital stays, liver-related outpatient laboratory tests, other outpatient laboratory tests, and outpatient internal medicine clinic visits (includes gastroenterology and infectious diseases clinics).

Differences in Mean Direct Medical Costs

Table 3 shows the adjusted differences in mean annual costs of the non-SVR group compared with the SVR group. Overall, patients without SVR incurred significantly higher annual post-treatment costs than did those who achieved SVR. This was observed for all categories analyzed, regardless of HCV genotype. Hospital costs did not show significant adjusted differences between the 2 groups. However, outpatient costs overall and by category showed significantly higher costs in the non-SVR group than in the SVR group, again regardless of HCV genotype.

Proportional Differences in Mean Direct Medical Costs

To further evaluate cost differences, we calculated the adjusted RRs of costs of patients in the non-SVR group compared with the SVR group. Adjusted RRs revealed that total costs for the non-SVR group were significantly higher (26%-64%) than those of the SVR group during each of post-treatment years 1 to 5 (Figure 2). For total and hospital costs, the adjusted RRs were greater than 1.0 for all years, and the increases were greater in the first year post-treatment.

RR (non-SVR compared with the SVR group) increased from years 1 to 3 post-treatment. By year 4, this increasing trend in cost differences appeared to taper off, although adjusted RR for total costs remained significant and over 1.4. When considering total outpatient post-treatment cost differences (i.e., excluding hospitalizations), the adjusted RRs for the non-SVR versus SVR group ranged by year from 1.18 to 1.34 (all outside

### Table 1

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>SVR (n = 927)</th>
<th>Non-SVR (n = 997)</th>
<th>P Value*</th>
<th>Total (n = 1,924)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SVR status</td>
<td></td>
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<tr>
<td>SVR</td>
<td></td>
<td></td>
<td></td>
<td>927 (48.2)</td>
</tr>
<tr>
<td>Non-SVR</td>
<td></td>
<td></td>
<td></td>
<td>997 (51.8)</td>
</tr>
<tr>
<td>Post-treatment</td>
<td></td>
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<tr>
<td>follow-up (years)</td>
<td>2.97 ± 1.44</td>
<td>2.94 ± 1.49</td>
<td>0.66</td>
<td>2.96 ± 1.47</td>
</tr>
<tr>
<td>Diabetes†</td>
<td></td>
<td></td>
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<td>226 (11.8)</td>
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<tr>
<td>History of cirrhosis‡</td>
<td>54 (5.8)</td>
<td>149 (14.9)</td>
<td>&lt;0.001</td>
<td>203 (10.6)</td>
</tr>
<tr>
<td>Quintile of pretreatment costs ($)§</td>
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<tr>
<td>1</td>
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<td>5</td>
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</table>

*P values for chi-square statistic (categorical data) and t-test for continuous measures.
†Most recent to treatment start.
‡Prior to treatment.
§Cut-points for quintile of pretreatment costs ($) — quintile 1: ≤ 2,561; 2: 2,562-3,788; 3: 3,789-5,235; 4: 5,236-8,481; 5: ≥ 8,482.
HCV = hepatitis C virus; SD = standard deviation; SVR = sustained virologic response.

RR (non-SVR compared with the SVR group) increased from years 1 to 3 post-treatment. By year 4, this increasing trend in cost differences appeared to taper off, although adjusted RR for total costs remained significant and over 1.4. When considering total outpatient post-treatment cost differences (i.e., excluding hospitalizations), the adjusted RRs for the non-SVR versus SVR group ranged by year from 1.18 to 1.34 (all
P<0.03; see Appendix A, available online). The differences in outpatient costs, while still statistically significant, appeared to plateau by year 2 and then taper off by years 4-5. Based on the adjusted RR for nonpharmacy outpatient costs, the non-SVR group incurred significantly higher costs in this category than did the SVR group during post-treatment years 1-3 (Figure 2). For outpatient pharmacy costs, significant adjusted RRs were found for each year (ranging from 1.2 to 1.8 by year) for the non-SVR group compared with those who achieved SVR. While we observed no statistically significant differences over time in the SVR effect within any cost category, an increasing trend for outpatient pharmacy was evident (P=0.26; Figure 2).

Table 4 shows the adjusted RRs for mean annual costs (all years combined) for the full cohort and stratified by HCV genotype (1 versus 2/3). In summary, compared with those who attained SVR, adjusted total, hospital, and outpatient costs for patients in the non-SVR group were 1.4, 1.7, and 1.4 times higher, respectively (all P<0.01). We observed similar and significant patterns for patients in both HCV genotype groups although the differences were somewhat more pronounced for patients with genotype 2/3 (versus 1).

Post-Treatment Health Services Utilization

We sought to further understand the observed cost differences between patients with and without SVR by comparing selected health care utilization in the post-treatment period. Figure 3 shows results from Poisson regression models comparing relative utilization rates of the non-SVR group compared with the SVR groups, adjusting for key factors. In post-treatment years 2-5, overall (not shown) and liver-specific laboratory test rates were approximately 60% to 80% and 70% to 130% higher, respectively, in the non-SVR group compared with those who attained SVR (P<0.001 for each year of follow-up time). Internal medicine (including gastroenterology and infectious diseases) clinic visit rates were 20% to 40% higher in the non-SVR group compared with SVR patients in years 2-5 after treatment (P<0.001 for those years). Hospitalization rates fluctuated by post-treatment year from 10% to 145% higher in the non-SVR group compared with SVR patients. There were statistically significant differences in SVR effect over time for liver-related lab tests, other lab tests, and internal medicine outpatient visits. In particular, there was a strong increasing trend in adjusted RR for liver-related lab tests (see Appendix B, available online).

Discussion

This study found that health care utilization rates and direct medical costs up to 5 years after HCV antiviral therapy were significantly higher among patients who did not achieve SVR than among those achieving viral clearance. Rates of hospitalization following treatment completion were higher among non-SVR patients than those with SVR, although small numbers...
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FIGURE 2 Rate Ratios for Incurred Costs by Post-Treatment Year: Non-SVR Group Compared with SVR Group

<table>
<thead>
<tr>
<th>Category of Cost ($)</th>
<th>Total</th>
<th>Hospital</th>
<th>Outpatient Nonpharmacy</th>
<th>Outpatient Pharmacy</th>
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<td>1.84</td>
<td>1.84</td>
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</table>

*Rate ratios of non-SVR group relative to SVR group graphed on logarithmic scale. Values above each bar represent the rate ratio. Bars represent 95% CIs.

P=0.68b

P=0.9b

P=0.11b

P=0.26b

TABLE 4 Post-Treatment Costs Incurred: Rate Ratios for Non-SVR Versus SVR Group

<table>
<thead>
<tr>
<th>Category of Costs</th>
<th>Total Cohort (n=1,924)</th>
<th>HCV Genotype</th>
<th>Total Cohort (n=1,924)</th>
<th>HCV Genotype</th>
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<tbody>
<tr>
<td></td>
<td>Adjusted Rate Ratio (95% CI)</td>
<td>P Value</td>
<td>Adjusted Rate Ratio (95% CI)</td>
<td>P Value</td>
</tr>
<tr>
<td>Total</td>
<td>1.41 (1.17-1.69)</td>
<td>&lt;0.001</td>
<td>1.30 (1.11-1.54)</td>
<td>0.010</td>
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<td>Hospital</td>
<td>1.66 (1.18-2.34)</td>
<td>&lt;0.001</td>
<td>1.41 (1.01-1.97)</td>
<td>0.045</td>
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<tr>
<td>Outpatient</td>
<td>1.41 (1.09-1.82)</td>
<td>0.009</td>
<td>1.21 (1.08-1.35)</td>
<td>0.004</td>
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<td>Nonpharmacy</td>
<td>1.26 (1.16-1.37)</td>
<td>&lt;0.001</td>
<td>1.20 (1.07-1.33)</td>
<td>0.008</td>
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<td>Pharmacy</td>
<td>1.39 (1.16-1.66)</td>
<td>&lt;0.001</td>
<td>1.29 (1.07-1.55)</td>
<td>0.012</td>
</tr>
</tbody>
</table>

*Adjusted for age, sex, race/ethnicity, cirrhosis history, pretreatment costs. Modeled as repeated measures using generalized estimating equations (GEE); log-linear models under gamma distribution.

CI=confidence interval; HCV=hepatitis C virus; SVR=sustained virologic response.
about disease progression and health care costs of patients with hepatitis C. Certainly, the cost of hepatitis patient care increases as liver disease severity progresses. Given that SVR serves to slow HCV-associated disease progression, our findings of lower post-treatment health care costs and utilization are both plausible and predictable.

A recent study compared health care costs among treated hepatitis C patients with and without SVR in the 6 months immediately following the end of treatment. They reported that patients not achieving SVR incurred about twice the total monthly costs of those with SVR ($717 vs. $1,436; P < 0.001); the differences were largely attributable to hospital costs. While the general conclusions are consistent with our findings, the results of Davis et al. suggest a more marked difference in costs between the 2 groups in the first year after treatment than we found. The small number but large relative contribution to costs of hospitalizations in both studies limits a useful comparison. Davis et al. reported no significant differences in office visits, other outpatient services, or laboratory tests during the immediate post-treatment period studied. This is consistent with our findings of the smallest differences in health care costs between SVR groups in the first year post-treatment. Regardless of response status, patients may be tested and managed for lingering treatment side effects (e.g., anemia, depression) in the months following treatment. Patients with undetectable HCV at the end of treatment, most of whom will be defined as SVR, are being seen for response-defining HCV RNA testing 24 weeks later.

With the advent of novel HCV antivirals with higher SVR rates compared with older therapies, and higher costs, it is important to contextualize the benefits of SVR when evaluating cost-effectiveness. Due to the typically slow progression of liver disease among the portion of patients developing complications from HCV infection, the estimated cost-effectiveness for HCV treatment may improve with increasing length of post-treatment time. Despite such projected longer term benefits of therapy, payers may consider the value of therapies primarily in the short term, consistent with 1- to 2-year budget
timelines. SVR appears to confer shorter-term economic benefits such as reductions in health care resource use for managing and monitoring HCV infection.

Limitations
We did not include never-infected control or untreated hepatitis C patients, and thus did not address the health care utilization or costs in those groups. Our study focused on all-cause costs and utilization; we did not attempt to distinguish events specifically related to liver health. However, since the study was limited to patients treated for hepatitis C and we used adjustment for utilization (through costs) prior to treatment, we believe the cost differences and RRs are reflective of the effects of viral clearance in this population. Certainly some factors affecting liver disease progression (and associated utilization and cost) are also predictors of SVR. Our models control for the major factor, baseline cirrhosis, as well as demographic factors such as age and sex. Additionally, comorbid conditions such as diabetes are accounted for, at least in part, by the adjustment for pretreatment cost. Of course, some confounding by predictors of SVR may still be present in the findings, but we posit that this is minimal.

Although our study was conducted retrospectively, its reliance on comprehensive electronic records allowed for complete assessment of a large number of patients, thus giving increased precision to our point estimates. Negligible, if any, misclassification of treatment response status is suspected since laboratory records and strict definitions of SVR were used. In addition, individuals with unknown SVR status (n = 200) were excluded; how these patients might differ from those included and how their exclusion impacted the results is unknown. Importantly though, the design remains subject to confounding by factors that influence the likelihood of SVR. Many such factors (race, cirrhosis, sex, age) were adjusted for in the models, minimizing bias related to these characteristics. However, factors not observable in the database such as drug and alcohol use or socioeconomic factors may have introduced some bias in results.

As expected with this study design in a health plan membership population, attrition of the study cohort occurred. The majority of attrition was due to maximal follow-up at December 31, 2008, leading to incremental reductions in sample size over the 5-year follow-up period (Figure 1). Just 16% of patients were lost to follow-up due to disenrollment from the health plan, ranging from 3% to 7% per follow-up year. Because the distributions of patient characteristics considered were similar in the cohorts over time, we believe that there are no systematic differences introduced by the attrition.

Although few patients were hospitalized in this study, hospital stays were a major contributor to cost and to the differentiation of costs between SVR and non-SVR patients. The low number of hospital events, and the high variance in the cost of such events, contributes to the imprecision of hospitalization rate and cost estimates. Hospitalization rates and costs were driven by events occurring among just 20% of the cohort. Furthermore, the most expensive outlier costs overall were attributable to hospitalizations. In absolute terms, the post-treatment rate of hospital admissions for the SVR cohort was 0.09 per person per year versus 0.16 among those not achieving SVR (unadjusted RR = 1.75; P < 0.001). However, these numbers should be considered in the context of the small number of events. Nonhospital costs offer more robust comparisons, given that almost every cohort member (98%) had such costs in each post-treatment year. We did find significantly higher adjusted total outpatient costs in the non-SVR group (versus the SVR group) in each post-treatment year.

Conclusion
Our study suggests that among patients treated for hepatitis C, SVR may be associated with significant reductions in future health care resource use and costs. Specifically, the findings reveal economic benefits of SVR within the first 5 years after treatment. Additionally, selected findings may be applied to other settings to estimate the potential impact of the successful treatment of hepatitis C on subsequent health care costs and utilization.

Authors
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DISCLOSURES
This study was funded by Vertex Pharmaceuticals Incorporated. Manos, Darbinian, and Shvachko report that they have received grants from Vertex, Merck, Roche, and Gilead; Ray reports that he has received grants from Vertex, Pfizer, Merck, GlaxoSmithKline, and Purdue; and Quesenberry reports that he has not received any funding. The other authors have not disclosed any funding related to this article other than from Vertex Pharmaceuticals.

Study concept and design were contributed primarily by Manos, with assistance from Quesenberry, Deniz, Ray, Darbinian, and Velez. Darbinian had primary responsibility for data collection, with assistance from Shvachko; data interpretation was the work of Manos, Quesenberry, Ray, Darbinian, Deniz, and Rubin. The manuscript was written primarily by Manos, with assistance from Darbinian and input from Quesenberry, Rubin, and Deniz and was revised primarily by Manos with input from Quesenberry, Ray, Darbinian, and Rubin.
ACKNOWLEDGMENTS

We thank Rosemary Murphy for help with tables and graphics and Bruce Fireman for helpful discussions.

REFERENCES

### Adjusted Rate Ratios of Costs Incurred, Non-SVR Compared with SVR Group, by Year Post-Treatment

<table>
<thead>
<tr>
<th>Category of Costs</th>
<th>Post-Treatment Year</th>
<th>N</th>
<th>Adjusted Rate Ratio, non-SVR vs. SVR (95% CI)</th>
<th>P Value</th>
<th>P Value for Test of Heterogeneity Over Time</th>
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<tr>
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<td></td>
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<tr>
<td><strong>Total</strong></td>
<td>1</td>
<td>1,924</td>
<td>1.26 (1.13-1.40)</td>
<td>&lt;0.001</td>
<td>0.685</td>
</tr>
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<td>1,488</td>
<td>1.44 (1.25-1.65)</td>
<td>&lt;0.001</td>
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<tr>
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<td>3</td>
<td>1,110</td>
<td>1.64 (1.38-1.96)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>746</td>
<td>1.41 (1.14-1.73)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>425</td>
<td>1.46 (1.11-1.93)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td><strong>Hospital</strong></td>
<td>1</td>
<td>1,924</td>
<td>1.47 (1.12-1.94)</td>
<td>0.006</td>
<td>0.900</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>1,488</td>
<td>1.59 (1.14-2.21)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>1,110</td>
<td>2.10 (1.39-3.18)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>746</td>
<td>2.08 (1.28-3.38)</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>425</td>
<td>1.10 (0.57-2.11)</td>
<td>0.781</td>
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<tr>
<td><strong>Outpatient</strong></td>
<td>1</td>
<td>1,924</td>
<td>1.18 (1.09-1.28)</td>
<td>&lt;0.001</td>
<td>0.089</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>1,488</td>
<td>1.31 (1.17-1.46)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>1,110</td>
<td>1.34 (1.17-1.52)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>746</td>
<td>1.21 (1.02-1.43)</td>
<td>0.029</td>
<td></td>
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<tr>
<td></td>
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<td>425</td>
<td>1.28 (1.03-1.60)</td>
<td>0.028</td>
<td></td>
</tr>
<tr>
<td><strong>Nonpharmacy</strong></td>
<td>1</td>
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<td>1.18 (1.09-1.28)</td>
<td>&lt;0.001</td>
<td>0.113</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>1,488</td>
<td>1.31 (1.17-1.48)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>1,110</td>
<td>1.30 (1.13-1.50)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>746</td>
<td>1.08 (0.91-1.29)</td>
<td>0.380</td>
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<td>425</td>
<td>1.18 (0.92-1.50)</td>
<td>0.191</td>
<td></td>
</tr>
<tr>
<td><strong>Pharmacy</strong></td>
<td>1</td>
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<td>1.16 (1.02-1.31)</td>
<td>0.022</td>
<td>0.257</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>1,488</td>
<td>1.27 (1.09-1.47)</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>1,110</td>
<td>1.45 (1.22-1.74)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>746</td>
<td>1.77 (1.41-2.22)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>425</td>
<td>1.84 (1.35-2.49)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

*These data are the basis for Figure 2. Log-linear models under gamma distribution. Adjusted for age at end of treatment, sex, race/ethnicity, history of cirrhosis prior to start of treatment, and quintile of pretreatment costs. P value from time (year post-treatment) x SVR group interaction term, repeated measures/GEE models using gamma distribution.

CI = confidence interval; GEE = generalized estimating equations; SVR = sustained virologic response.
## The Effect of Hepatitis C Treatment Response on Medical Costs: A Longitudinal Analysis in an Integrated Care Setting

### APPENDIX B

**Adjusted Rate Ratios for Health Care Utilization, Non-SVR Compared with SVR Group, by Year Post-Treatment**

<table>
<thead>
<tr>
<th>Category of Utilization</th>
<th>Post-Treatment Year</th>
<th>N</th>
<th>Adjusted Rate Ratio, non-SVR vs. SVR (95% CI)</th>
<th>P Value</th>
<th>P Value for Test of Heterogeneity Over Time</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Outpatient lab tests</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>1</td>
<td>1,924</td>
<td>1.10 (1.02-1.19)</td>
<td>0.013</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>1,488</td>
<td>1.59 (1.42-1.78)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>1,110</td>
<td>1.58 (1.37-1.83)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>746</td>
<td>1.59 (1.31-1.93)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>425</td>
<td>1.78 (1.41-2.20)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Liver-related</td>
<td>1</td>
<td>1,924</td>
<td>1.10 (1.03-1.19)</td>
<td>0.006</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>1,488</td>
<td>1.69 (1.51-1.88)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>1,110</td>
<td>1.80 (1.55-2.09)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>746</td>
<td>2.05 (1.70-2.48)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>425</td>
<td>2.31 (1.79-2.98)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Other lab tests</td>
<td>1</td>
<td>1,924</td>
<td>1.10 (1.01-1.19)</td>
<td>0.020</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>1,488</td>
<td>1.57 (1.40-1.77)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>1,110</td>
<td>1.55 (1.34-1.79)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>746</td>
<td>1.53 (1.25-1.85)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>425</td>
<td>1.71 (1.35-2.17)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Hospitalizations (# admissions)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1,924</td>
<td>1.61 (1.29-2.02)</td>
<td>&lt;0.001</td>
<td>0.565</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>1,488</td>
<td>1.10 (0.87-1.40)</td>
<td>0.431</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>1,110</td>
<td>1.65 (1.25-2.18)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>746</td>
<td>1.46 (1.05-2.03)</td>
<td>0.025</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>425</td>
<td>2.45 (1.56-3.85)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Outpatient encounter (# visits)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Internal medicine</td>
<td>1</td>
<td>1,924</td>
<td>1.05 (0.97-1.13)</td>
<td>0.200</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>1,488</td>
<td>1.39 (1.25-1.54)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>1,110</td>
<td>1.36 (1.20-1.54)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>746</td>
<td>1.27 (1.09-1.49)</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>425</td>
<td>1.19 (0.98-1.45)</td>
<td>0.079</td>
<td></td>
</tr>
</tbody>
</table>

*These data are the basis for Figure 3. Adjusted for age at end of treatment, sex, race/ethnicity, total costs one year prior to start of anti-viral therapy (modeled as quintiles), and history of cirrhosis prior to starting treatment. P value from time (year post-treatment) x SVR group interaction term, repeated measures/GEE models using Poisson distribution and scaling for over-dispersion of data.

CI = confidence interval; GEE = generalized estimating equations; SVR = sustained virologic response.
Antiviral Regimen Complexity Index as an Independent Predictor of Sustained Virologic Response in Patients with Chronic Hepatitis C

Rocio Jiménez Galán, BS; Elena Calvo Cidoncha, BS; Mónica Ferrit Martin, BS; Concepción Carrascosa Rodríguez, BS; Carmen V. Almeida González, MS; Ramón Morillo Verdugo, BS

ABSTRACT

BACKGROUND: Hepatitis C virus (HCV) infection affects more than 170 million people worldwide, and one-third of them have human immunodeficiency virus (HIV) coinfection. Multiple studies have been conducted in order to identify the factors that may explain different responses to treatment among patients. However, the reasons why HIV-HCV coinfected patients have lower responses to treatment are not clear. In addition, no studies have evaluated the influence of the complexity of the therapeutic regimen for hepatitis C infection on clinical outcomes.

OBJECTIVES: To (a) investigate the influence of the antiviral regimen complexity in the sustained viral response (SVR) in patients with chronic hepatitis and (b) adapt a method of quantifying complexity of an antiretroviral regimen for patients infected with HCV.

METHODS: A single center, retrospective study was conducted in HCV and HIV-HCV coinfected patients. We selected patients treated with interferon alfa-2a plus ribavirin between January 2005 and December 2010. Patients with severe psychiatric disorders, those included in a clinical trial, and those known to be nonadherent to treatment were excluded. The dependent variable was the sustained virologic response and the independent variables were sex, age, race, stage fibrosis (F), presence or absence of cirrhosis, low hepatitis C baseline viral load (defined as ≥800,000 IU), viral genotype, rapid virological response (RVR), serum gamma-glutamyltransferase (GGT) levels, ratio of alanine aminotransferase to aspartate aminotransferase (ALT/AST), serum cholesterol level, presence or absence of diabetes mellitus, and antiviral regimen complexity index. The latter variable included drugs for HCV and HIV infection, but no medication for other comorbidities. To evaluate the complexity of antiviral treatment we performed an adaptation of the system developed by Martin et al. (2007) in HIV patients. The factors determining the complexity of treatment were the number of medications, dosing schedules, administration methods, special instructions, and required preparations associated with antiviral regimens. Sample size was estimated by the Freeman equation. To determine the independent variables associated with SVR, we performed an univariate logistic regression and subsequently a multivariate analysis with those variables that demonstrated a statistically significant difference in the univariate analysis.

RESULTS: A total of 156 patients was included (76% men, mean age 44 years) of whom 45% were HIV-HCV coinfected. 75% were genotypes 1 or 4. The univariate analysis variables—genotypes 2 and 3 (OR = 3.10; CI [1.38-6.95]; P = 0.006); HIV-HCV coinfecion (OR = 0.36; CI [0.19-0.69]); presence of cirrhosis (OR = 0.27; CI [0.10-0.73]; P = 0.01); F ≥ 2 (OR = 0.44; CI [0.23-0.84]; P = 0.01); low baseline viral load (OR = 2.05; CI [1.01-4.17]; P = 0.048); RVR (OR = 17.60; CI [6.84-45.30]; P < 0.001); complexity index (OR = 0.71; CI [0.58-0.87]; P = 0.001), showed statistically significant relationships with SVR. Complexity index (OR = 0.67; CI [0.52-0.87]; P = 0.002) and RVR (OR = 20.04; CI [7.33-54.85]; P < 0.001) were independent predictors of SVR in multivariate analysis. The reliability of the multivariate analysis was checked with the Hosmer and Lemeshow test (P = 0.079).

CONCLUSIONS: The medication regimen complexity may be a crucial factor to achieve therapeutic success when treating patients for hepatitis C. The adaptation of this index in patients with HCV provides an objective value of the antiviral regimen complexity and could help us to identify patients in clinical practice who require multidisciplinary attention. Simplification of the antiretroviral regimen might result in a greater response to treatment for hepatitis C.


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Antiviral Regimen Complexity Index as an Independent Predictor of Sustained Virologic Response in Patients with Chronic Hepatitis C

Hepatitis C virus (HCV) infection affects more than 170 million people worldwide, with one-third of them presenting with human immunodeficiency virus (HIV) coinfection. HCV is a major public health problem worldwide, causing one million deaths annually.1

Until 2011, the standard therapy for the treatment of hepatitis C was based on the combination therapy of pegylated interferon (pegINF) alfa-2a or alfa-2b and ribavirin (RBV) administered for 24 or 48 weeks. The recent emergence of direct antiviral agents has caused a radical change in the prognosis of the disease.3

The goal of treatment of hepatitis C infection is to eradicate the virus, thus preventing disease progression to cirrhosis and reducing the risk of hepatocellular carcinoma. The biomarker that best correlates with a cure is the achievement of sustained virologic response (SVR),4 defined as a negative HCV ribonucleic acid (RNA) 6 months after completing the antiviral treatment.

Over the past few years several studies have identified clinical, virologic, histologic, biochemical, and demographic features that can predict a lower response to treatment with pegINF and RBV.5-7 However, we still do not know all the variables that may explain different responses among patients. The rapid virological response (RVR), defined as an undetectable hepatitis C viral load 4 weeks after the beginning of treatment, has been one of the factors most strongly associated with the achievement of SVR.8-10 HIV-HCV coinfected patients have lower rates of HCV SVR compared with monoinfected patients (40% vs. 54-63%, respectively). Although the causes of lower response still remain unclear, coinfected patients have higher baseline viral loads and faster progression of the disease to liver fibrosis, as well as an increased risk of cirrhosis and hepatocellular carcinoma.11 Adherence to combination therapy is known to be a crucial factor in achieving early virologic response (EVR) and subsequently SVR.12,13 Mechanisms that may improve adherence to therapy include pharmacologic management of treatment-related adverse effects and careful selection, monitoring, and education of patients.

Pharmacists are in an ideal position to provide care for patients with HCV due to the long duration of therapy, need for close monitoring of adverse effects and laboratory values, and potential dose adjustments required.14 Studies have suggested that coordinated care between pharmacists and physicians improves patient care outcomes.15 Since the emergence of the concept of pharmaceutical care in Spain, hospital pharmacy departments have implemented this activity. Therefore, pharmaceutical care plays a key role in detecting drug-related problems and the development of measures to prevent them.16 In order to do so, it is necessary to have specialized pharmacists and to create disease-specific clinics. Medication regimen complexity could be another key factor, which has not yet been considered in clinical practice. In 2011, the American Society of Health-System Pharmacists published a consensus document about optimal pharmacy practice models in hospitals and health systems.17 One of the specific points mentioned in this consensus was that pharmacist-provided drug therapy management should be prioritized using a patient medication complexity index. However, validated methods to quantify regimen complexity need to be developed. Martin et al. (2007) developed a method for quantifying antiretroviral regimen complexity (ARC) in HIV patients.18

Multiple studies have been conducted in patients with HCV infection in order to identify the factors that may explain the different responses to treatment among patients. The reasons why HIV-HCV coinfected patients have lower responses to treatment are not yet clearly understood.19 No studies have evaluated the influence of the complexity of the therapeutic regimen for hepatitis C infection on clinical outcomes. Therefore, the main objective of this study is to determine the influence of therapeutic regimen complexity on the achievement of SVR in HCV-infected patient, and to adapt a complexity index for this population based on the premise established by Martin et al. for patients with antiretroviral treatment.

Methods

We conducted a retrospective observational study that included HCV monoinfected patients and HIV-HCV coinfected patients who attended the pharmaceutical care office of a pharmacy service, which initiated treatment with pegINF and RBV between January 2005 and December 2010. We excluded patients enrolled in clinical trials, those with psychiatric disorders that may affect treatment adherence, and patients whose data were not available.

SVR was considered the dependent variable. We also collected the following demographic and clinical parameters described in the literature as independent predictors of SVR: age, sex, race, HIV-HCV coinfection, baseline cirrhosis, diabetes mellitus, significant fibrosis (F ≥ 2), viral load (international units per milliliter [IU/mL]), serum gamma-glutamyltransferase (GGT; IU/L), ratio of alanine aminotransferase to aspartate aminotransferase (ALT/AST), total cholesterol (milligram per deciliter [mg/dL]), RVR, and viral genotype. In addition, an antiviral treatment complexity index was calculated for each patient.

This complexity index was calculated through the application available in Spanish at: http://www.farmaciamcp.com/consulta/actividad/indice-de-complejidad/, based on an adaptation of the score created by Martin et al.18 and whose items include the number of pills per day, the dosing schedule, dosage form, and specific instructions associated with taking drugs. The medication was obtained from a pharmacy dispensing program to outpatients.

The remaining variables were obtained by consulting analytics, microbiology reports, and from review of the medical history of each patient. Continuous variables were expressed...
Antiviral Regimen Complexity Index as an Independent Predictor of Sustained Virologic Response in Patients with Chronic Hepatitis C

TABLE 1  Baseline and Clinical Characteristics of the Patients Included in the Study

<table>
<thead>
<tr>
<th>Variable</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex: male/female (% male)</td>
<td>119/37 (76)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>45 ± 8.01</td>
</tr>
<tr>
<td>Caucasian race: n (%)</td>
<td>156 (100)</td>
</tr>
<tr>
<td>HIV-HCV coinfection: n (%)</td>
<td>70 (45)</td>
</tr>
<tr>
<td>Significant fibrosis (F ≥ 2): n (%)</td>
<td>72 (46)</td>
</tr>
<tr>
<td>Cirrhosis: n (%)</td>
<td>22 (14)</td>
</tr>
<tr>
<td>Diabetes mellitus: n (%)</td>
<td>30 (19)</td>
</tr>
<tr>
<td>AST (IU/L)</td>
<td>50 ± 115</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>166 ± 37.8</td>
</tr>
<tr>
<td>ALT/AST</td>
<td>0.9 ± 0.4</td>
</tr>
<tr>
<td>Genotype 1/4: n (%)</td>
<td>117 (75)</td>
</tr>
<tr>
<td>Viral load &gt;800,000 IU/mL (%)</td>
<td>109 (70)</td>
</tr>
<tr>
<td>RVR: n (%)</td>
<td>58 (37)</td>
</tr>
<tr>
<td>SVR: n (%)</td>
<td>91 (58)</td>
</tr>
<tr>
<td>Complexity index</td>
<td>8.68 ± 1.62</td>
</tr>
</tbody>
</table>

ALT/AST = ratio of alanine aminotransferase to aspartate aminotransferase; AST = aspartate aminotransferase; HCV = human immunodeficiency virus; Hepatitis C virus; IU/L = international units per liter; mg/dL = milligrams per deciliter; RVR = rapid viral response; SVR = sustained viral response.

as the mean value and standard deviation (SD) and categorical variables as percentages (%), calculating a 95% confidence interval (CI) when necessary.

We developed a multivariate logistic regression model that identified the role of pharmacotherapy complexity index as an independent variable predictive of SVR. The sample size was estimated according to the Freeman equation, 10 × (k + 1), where k expresses the number of covariates. However, in case of dichotomous variables, there must be at least 10 cases for each of the possible values. As the population was homogeneous, we had to gather a similar percentage of patients monoinfected and coinfected. To know the relationship between each of the variables and SVR rate, we performed a logistic regression analysis. Subsequently, a multivariate analysis was performed by likelihood ratio. Variables that had shown statistical significance in the logistic regression were included as well as confounding variables such as age and sex. Validity of the model was evaluated in both cases by the Hosmer and Lemeshow test. Data analysis was performed using the statistical package SPSS 20.0 for Windows (SPSS, Inc., Chicago, IL).

Results

We included 156 patients in the study, whose baseline and clinical characteristics are detailed in Table 1. As noted, all patients were Caucasian, most were men, and the mean age was 44 years. Regarding clinical characteristics, the number of HIV-HCV coinfected patients and the number of patients with significant fibrosis were similar and approached 50% of the population. In contrast, the percentage of patients with cirrhosis and diabetes was low. Average cholesterol levels were within the normal range. However, the mean values of GGT were above normal limits. The majority (75%) of patients were infected with viral genotype 1 or 4. High viral load occurred in a high percentage (70%) of patients. On the other hand, 37% of patients achieved RVR, and SVR was achieved in 54% of patients. The mean complexity index was $9.13 ± 1.72$.

The percentages of mono- and coinfect patients according to the complexity index values calculated are shown in Figure 1. The complexity index values were lower in monoinfected patients, ranging from 7.25 to 9.75, compared with coinfected patients, whose values reached 13.25. The complexity index variability in patients was due mainly to the number of pills per day, number of pills per dose, and specific instructions associated with taking drugs (with food or on an empty stomach). Patients with more complex regimens were those treated with HIV protease inhibitors, followed by those treated with zidovudine, didanosine, raltegravir, and maraviroc. However, etravirine did not have a high complexity index because it can be taken in a single dose, which facilitates administration. However, patients treated with atiprila (coformulation efavirenz/emtricitabine/tenofovir) had a similar complexity index to that of monoinfected patients.
Table 2 includes the rates of SVR according to demographic, virologic, and histologic characteristics. Regarding the qualitative variables, there are major differences in SVR rates according to clinical characteristics. Regarding the qualitative variables, there are major differences in SVR rates according to clinical characteristics. Thus, 90% of patients with RVR achieved SVR. Other important variables were the presence of cirrhosis (58% without cirrhosis achieved SVR vs. 27% with cirrhosis) and viral genotype (74% with genotype 2 or 3 achieved SVR vs. 48% for genotype 1 or 4). On the other hand, values of GGT and AST/ALT ratio were higher in patients who did not achieve SVR, reflecting increased hepatic progression among patients who had not responded to treatment. Similarly, the average value of the complexity index was higher in patients who did not achieve SVR.

The limited presence of diabetes mellitus in the study population (3 patients) led to the exclusion of this variable in the logistic regression analysis. Variables that reached statistical significance with the SVR rate in the univariate regression analysis were genotype 2 or 3, HCV monoinfection, low viral load (≤800,000 IU/mL), no cirrhosis, no significant fibrosis, achievement of RVR, and lower complexity index. Table 3 shows the relationship between these variables and the SVR expressed by the odds ratio for a confidence interval of 95%. The value of the Hosmer and Lemeshow test confirmed the validity of this model (P = 0.606).

Subsequently, multivariate analysis showed that RVR and the complexity index were the only independent predictors of SVR (Table 4). Similarly, the Hosmer and Lemeshow test showed the validity of the analysis (P = 0.079) despite not having achieved the sample size estimate.

### Discussion

In our study, the complexity index was identified as a predictor of SVR. The variables that showed statistically significant relationships with the SVR were consistent with the results obtained in previous studies. However, in the multivariate analysis, only RVR and the complexity index were identified as independent predictors of response. The influence of the complexity of medication regimen on response to treatment for hepatitis C has not previously been evaluated.

Also, in this study we have adapted a system that has allowed us to quantify antiviral regimen complexity. This system was initially developed for other patient populations, such as HIV-infected and elderly patients. However, no studies have been conducted in patients with hepatitis C.

As in many other chronic illnesses with detrimental sequelae, pharmacists may be a resource to manage the disease and mitigate negative outcomes. In fact, the role of pharmacists in optimizing treatment response and managing adverse effects in HCV infection is recognized. Marno et al. (2009) described the results of pharmacist interventions for optimizing response in treatment-naïve patients with chronic HCV-1. They noted that the SVR may be higher due to the low rate of early treatment discontinuation in the study. Additionally, the overall mean adherence rate was 85.7%; the adherence rate in the patients achieving SVR reached an impressive 95.5%. Therefore, this study shows that pharmacists can strongly influence patients with respect to education, adherence, and management of adverse effects. However, there are no tools for pharmaceutical care to optimize therapeutic results in patients.
with chronic hepatitis C. In our study, we propose a simple tool to be applied in the clinical practice of pharmacy departments.

To date, pharmaceutical activity has been based on adherence, but we include in our study the concept of medication regimen complexity. Adherence and complexity are closely linked, since adherence can be compromised by a high complexity of the treatment. Several studies have found that adherence is a key factor in achieving EVR and SVR.\textsuperscript{12,13,26}

The application of this tool in clinical practice will allow us to identify which patients have more complex treatments and require special attention by health care professionals and to help develop measures to ensure therapeutic success. Currently, the complexity index could play a key role due to the emergence of direct-acting antiviral agents that selectively target HCV, since the addition of these agents to the combination therapy of peg-IFN and RBV implies a significant increase in the complexity of treatment.\textsuperscript{27}

The main objective of the multidisciplinary team responsible for the care of HCV patients is to achieve therapeutic success. This requires the development of new pharmacotherapeutic tools for patient follow-up. Further studies are needed to explore the benefits of the pharmacist’s application of this tool in hepatitis C-infected patient management.

Limitations
The limitations of this study relate to the retrospective nature of the data and the difficulty in collecting all variables. This is the reason why the sample size was lower than estimated. However, the Hosmer and Lemeshow test confirmed the stability of the model, as well as the reliability and veracity of the results.

Adherence was not included as a variable in our study due to its retrospective design, but it was assessed through the electronic dispensing records from our pharmacy program, from which we excluded patients who did not regularly fill their prescriptions.

Inclusion of coinfected HIV-HCV patients could have been considered a complicating factor, since the response in these patients is lower, although the specific causes of this response are currently not known. To address this complication, we included the main predictors of SVR described in the literature and conducted a multivariate analysis. Nevertheless, the increased regimen complexity in coinfected patients may be one of the causes that would justify the lower response seen in this patient population. However, some coinfected patients included in our study had complexity indices similar to those of monoinfected patients. This may be due to the advancement of antiretroviral therapy in recent years.

Conclusions
Medication regimen complexity may be a crucial factor in achieving therapeutic success in the treatment of HCV. Pharmacists may apply this system of quantification to identify patients with more complex regimens and conduct measures to ensure that therapeutic goals are achieved. On the other hand, the simplification of highly active antiretroviral therapy in HIV-HCV coinfected patients could increase the response rates to the treatment of hepatitis C.

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DISCLOSURES
The authors report no financial conflicts of interest related to the subjects discussed in this article.

Concept and design were performed by Galán and Verdugo. Data were collected by Galán and Cidoncha and interpreted by Galán, Cidoncha, and González. The manuscript was written by Galán, Cidoncha, Martin, and Rodriguez and revised by Martin, Rodriguez and Verdugo.

REFERENCES


A Qualitative Study Examining HIV Antiretroviral Adherence Counseling and Support in Community Pharmacies

Jennifer Cocohoba, PharmD, MAS; Megan Comfort, PhD; Hamaseh Kianfar, PhD; and Mallory O. Johnson, PhD

ABSTRACT

BACKGROUND: Observational studies suggest that HIV-focused pharmacies can improve antiretroviral therapy (ART) refill adherence, but there is a lack of clear documentation about the kind and variability of adherence interventions that are conducted.

OBJECTIVE: To use qualitative research methods to obtain an in-depth understanding of how ART adherence support and counseling is provided in human immunodeficiency virus (HIV)-focused community pharmacies. To determine relevant facilitators and barriers around adherence support from both patient’s and pharmacist’s perspectives.

METHODS: A qualitative research study of patients who patronized and pharmacists who were employed at HIV-focused pharmacies in the San Francisco Bay Area was conducted. Participants were recruited using flyers at HIV clinics and community-based organizations and using blurbs in newsletters. Transcripts were analyzed using grounded theory methods to determine emergent themes in the data.

RESULTS: 19 eligible patients with a self-reported diagnosis of HIV, who were taking their current ART regimen for at least 3 months, and who obtained their ART from a community pharmacy in the San Francisco Bay Area were included; 9 pharmacists who were employed at 9 different pharmacy locations frequented by participants were interviewed. Emergent themes included descriptions of pharmacy adherence counseling and support, roles and responsibilities regarding medication adherence, barriers to providing adherence support, and feeling connected as a facilitator to adherence support relationships.

CONCLUSION: Pharmacists provide diverse types of ART adherence support and are uniquely positioned to help clients manage their medications. Additional training on developing relationships with patients and advertising their adherence services may further the role of community pharmacists in supporting antiretroviral adherence.

J Manag Care Pharm. 2013;19(6):454-60

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What this study adds

• This study examined HIV ART adherence support as specifically conducted in HIV-focused community pharmacies. Pharmacists interviewed in this study all reported serving a high volume of HIV-positive patients.
• This study elicited HIV patients' experiences and opinions on pharmacy ART adherence support. Examining both the pharmacist's and the patient's desires, needs, and perceptions regarding ART adherence support can give greater direction on changes that might be implemented to improve pharmacy practice.
• This study outlines some considerations for pharmacies that wish to provide HIV-focused services to their clientele such as the need for personalized engagement, training in behavior change techniques to improve adherence counseling, considerations for patient privacy, and linkages to other community-based HIV services.

C ommunity pharmacists create enhanced pharmacy service models to improve the health of patients with chronic diseases such as human immunodeficiency virus (HIV). These service models are often complex and typically comprise several combined interventions such as medication profile reviews, provision of patient medication records, and adherence support. They are typically assessed using quantitative outcomes; however, for pharmacy interventions that seek to improve medication adherence, qualitative research can add tremendous value. Qualitative research is an exploratory process that attempts to understand perceptions, beliefs, values, and attitudes that underlie an experience such as taking medications or visiting the pharmacy. Although it is more common to the social sciences, there are several applications for pharmacy practice research. Qualitative research can be used to gain an in-depth understanding of patient needs or work-flow processes when developing a clinical service. It can assess the barriers to implementation of a pharmacy service or the parts of a service that are perceived as essential by its users. It may be used prior to the development of a

What is already known about this subject

• Strict adherence to antiretroviral therapy (ART) at levels 95% or greater are desirable to keep human immunodeficiency virus (HIV) viral load suppressed to undetectable levels.15-16
• Studies have demonstrated that patients using HIV-focused community pharmacies have a 4.9%-22.1% higher mean refill adherence as measured by medication possession ratios or proportion of days covered compared with pharmacies that do not offer specialized HIV services. Typically, ART adherence interventions conducted in these studies are diverse and not well-documented.3-6
quantitative research survey to ensure that all important aspects are included for measurement. Qualitative research typically relies on interview or focus group data, de-emphasizes numerical counts, and often utilizes much smaller samples than are used in quantitative research.

For pharmacies serving patients with HIV, supporting optimal antiretroviral therapy (ART) adherence is essential for patients to maintain health, reduce potential for drug-resistant mutations, and reduce potential for HIV transmission. Recent studies found that patients using pharmacies with HIV-focused services had higher ART refill adherence compared with pharmacies that do not.1-4 These studies support pharmacy-based efforts to improve ART adherence. One of the challenges that remains with these large quantitative studies is a lack of clarity as to what comprises the adherence intervention or what the variability in the interventions is across sites.5 Our goal in conducting this qualitative research study was to develop a better understanding of the adherence support services that are offered in HIV-specialized pharmacies that serve a high-volume of HIV-positive patients. We hope that this study can provide valuable insight on the adherence support interventions commonly provided in pharmacies as well as patient and provider perceptions of those services. With this information, we will develop a framework for developing ART adherence services in community pharmacies.

Methods

Recruitment

HIV-positive subjects were recruited by posting flyers at the San Francisco Women’s Interagency HIV Study (WIHS) clinical study site, University of California San Francisco 360 Positive Care Center and Women's HIV Clinics, Catholic Charities Rita da Cascia Family House, and the Tenderloin Resource Center.6,7 A recruitment announcement was placed in the bimonthly WIHS Woman newsletter. Individuals were eligible if they had a self-reported diagnosis of HIV, were taking their current ART regimen for at least 3 months, and obtained ART from a community pharmacy in the San Francisco Bay Area. The criterion for taking ART for greater than 3 months was to ensure that participants had at least 3 recent opportunities to interact with their pharmacy. Patients who never went to a pharmacy and only utilized mail-order or pharmacy delivery services were excluded. Written informed consent was obtained, and subjects were consecutively recruited until saturation occurred (n = 19). Saturation is the phenomenon where no new themes emerge despite additional data collection.8

To recruit pharmacist study participants, flyers were posted at pharmacies utilized by the enrolled HIV-positive subjects. It became evident that many HIV-positive subjects used 3 specific HIV-focused community pharmacies in San Francisco. To ensure a diverse sample of pharmacists, we expanded recruitment to other HIV-focused pharmacies in the area and allowed pharmacists to contact their colleagues at other HIV-focused pharmacies and ask them to participate. Pharmacists had to be licensed and registered in California, self-report working in a pharmacy serving a high volume of HIV-positive patients, and give verbal consent in order to participate.

Interviews

A semistructured interview guide tailored to HIV-positive subjects and one tailored to pharmacists were designed for the study. Patient-participants were asked to describe their pharmacy, the staff, and their recent visit. Pharmacists were asked about their pharmacy career, their pharmacy, the patient population they serve, and which patients typically receive adherence support. Both groups were asked to describe their experiences with ART or providing ART adherence support, their opinions on the importance of this support, and barriers to communication around adherence. Questions are further detailed in the Appendix, which is available in the online article. Face-to-face interviews with HIV-positive subjects were performed in a private room by 1 investigator. Interviews took place within a 7-day window of the subject’s last pharmacy visit to minimize recall bias and ensure that the subject had a recent pharmacy interaction. If more than 7 days had passed since the last pharmacy visit, the interview was rescheduled. Subjects were offered a $25 gift card for their participation. Due to their busy schedules, pharmacists were interviewed via telephone and were offered a $50 honorarium for participating. All interviews were digitally audio-recorded and transcribed verbatim by a medical transcription company. The study was approved by the University of California, San Francisco Committee on Human Research.

Analysis

We used grounded theory methods to develop a conceptual framework for the research.9,10 Grounded theory searches for patterns, conducts iterative comparisons, and analyzes outlying cases in order to identify common themes among the data. Our primary interest was to examine the pharmacist-patient dynamic and facilitators and barriers of pharmacy-based ART adherence support. Transcripts were independently reviewed by 2 members of the research team using line-by-line techniques to identify common themes. A preliminary codebook was developed after reading the first 4 interviews; this codebook was refined using axial coding techniques as subsequent transcripts and new elements emerged. Data were imported into ATLAS.ti version 6.2, and the final codebook was applied to all of the data by one researcher.

Results

Participants

Nineteen HIV-positive subjects representing 13 different pharmacy locations participated in the semistructured interviews (see Table). All but 2 subjects resided in San Francisco; most had been using their pharmacy for an average of 4 years. Pharmacists (n = 9) recruited from 9 different HIV-focused
Table Participant Demographics

<table>
<thead>
<tr>
<th></th>
<th>Patient-Participants (n = 19)</th>
<th>Pharmacists (n = 9)</th>
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<tbody>
<tr>
<td>Male</td>
<td>11%</td>
<td>56%</td>
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<tr>
<td>Age (years), mean&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>—</td>
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<tr>
<td>Years practicing as a pharmacist, mean&lt;sup&gt;b&lt;/sup&gt;</td>
<td>—</td>
<td>10.4</td>
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<tr>
<td>Years going to current pharmacy, mean&lt;sup&gt;c&lt;/sup&gt;</td>
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<td>—</td>
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<tr>
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<td>White</td>
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<td>56%</td>
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<tr>
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<tr>
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<td>22%</td>
</tr>
<tr>
<td>Clinic-associated</td>
<td>11%</td>
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<sup>a</sup>Only asked of patient-participants.<br>
<sup>b</sup>Only asked of pharmacists.

Pharmacies had been practicing pharmacy for an average of 10 years (range: 3-28 years).

Emergent Themes Regarding Pharmacy Adherence Counseling and Support

The primary themes derived from the analyses included (a) descriptions of adherence support provided at HIV-focused pharmacies, (b) roles and responsibility for supporting ART adherence, (c) barriers to providing or accepting adherence support, (d) the feeling of being known by the pharmacy as a facilitator of adherence-supportive relationships, and (e) a need for training in effective adherence communication. Of note, participants and pharmacists often expressed views and experiences that encompassed all medication adherence support, not just specifically for ART.

Adherence Counseling and Support at HIV-Focused Pharmacies. Community pharmacies support ART adherence in multiple ways. Patients who are unable to access their medications due to insurance or other health-system delays are at risk for nonadherence. Patients often highlighted the pharmacist’s role in facilitating ART receipt as a very important tangible form of adherence support:

“There’s been times where I was waiting for a medication … and they gave me a couple of pills to hold me until it got okayed, and that’s always good to know that your pharmacist will do that for you.” (50-year-old white female)

“Sometimes I can say my doctor ordered something for me and my insurance doesn’t pay for it, so [the pharmacist] always says that she’s going to make sure I get what I need.” (43-year-old African American female)

Pharmacists mentioned other tangible forms of adherence support such as enrolling their patients in automatic refill programs, sending patients telephone or text refill reminders, synchronizing medication fill dates to streamline the number of trips that a patient made to the pharmacy to pick up medication, and preparation of reminder packaging such as medicine boxes or bubble packages. Pharmacists were confident that these services had a positive impact on adherence:

“I have patients that can be on 15 drugs per day … And so we try to get them all together at the same time in a timely manner.” (pharmacist, Asian male)

“… call the patient when their refill is due to remind them to come and pick it up, which is something we do, or send it to their house if they’re unable or unwilling to come to the pharmacy. If they’re not really picking up their medications all that often, I might try to figure out what’s going on, if they might want a bubble pack, you know, medi-set type thing to manage their medications a little bit better.” (pharmacist, white female)

Pharmacists stated that it was important to counsel patients on maintaining high adherence when dispensing new ART prescriptions. They also described some unsuccessful attempts to counsel poorly adherent patients and expressed mixed feelings regarding their communication effectiveness and doubt regarding patients’ openness to discussing antiretroviral adherence:

“For new patients, new consults, and patients who have just been diagnosed or just started their medications … our initial counseling always involves ‘It’s really important to take these on a regular basis’. And we kind of go through why it’s important, and how you can develop resistance, and then you’ll have to change regimens, and your virus is going to gain the upper hand.” (pharmacist, white female)

“So, I’ll go and talk to patients if I’ve noticed that they haven’t been picking up regularly, and I’ll just go and ask them if they’ve been getting it elsewhere or if they had an extra supply … Generally, the response is yes, I’ve had something somewhere. They don’t tend to admit that they haven’t been taking the medications, to me, at least … I don’t know if there’s a better way to approach someone to have them admit that they’re not taking them every day or they’re having trouble remembering taking them every day or they—yeah, if they are having adverse effects, they’re not saying that’s the problem.” (pharmacist, white female)

“Some of them just don’t want to hear you … Like ‘Okay, okay, okay. Yes, well, my doctor told me that already’, you know? … I mean, a lot of them are pretty okay with talking to me. They don’t really mind. But a lot of the times, they’re not really listening. They’re just saying okay.” (pharmacist, African American female)
Roles and Responsibility for Supporting a Patient's ART Adherence. Participants had different opinions on the pharmacist's responsibility to support ART adherence. Patients ascribed higher importance to medication dispensing and generally did not report that supporting adherence was a pharmacist’s responsibility. They had difficulty imagining how a pharmacist could have adequate time to support ART adherence because they expected them to spend a majority of their time focusing on dispensing medications correctly:

“I think that a pharmacist has their job cut out for them… I think it’s pretty much up to the person to take their medication. I mean, because if the pharmacist went around [calling everyone], he would have a pretty busy job. He’d have a 24/7 job. I mean, he can’t be on everybody for their medication … they’re busy, and they got to focus on keeping a clear mind on what they’re doing, making sure that the right medicine is getting in the right bottle, going to the right person. Because you make a mistake on somebody’s medication, somebody might be allergic to something, and you give them the wrong medication, you can be sued. You can kill somebody.” (50-year-old white female)

When patients delineated the team responsible for supporting ART adherence, they placed their own efforts at the center of the model and described a strong sense of personal responsibility to adhere. They expressed the importance of having a trusting partnership with their treating clinician to overcome adherence struggles. Most did not include their pharmacist as an integral member of the adherence team:

Interviewer: “Do you think it’s part of the pharmacist’s job to help people take their medicines every day?”

Respondent: “No. I think it’s up to the people. I think it’s up to their provider.” (43-year-old African American female)

“It’s up to me. It’s my job, because I want to live. Yes, I want to make my pharmacist proud of me that he’s doing his job well. He’s filling my medication well. I can go back and say, ‘Fill me up again. Give me another refill.’” (50-year-old white female)

On the contrary, pharmacists reported that detecting nonadherence and providing counseling and support was as important as dispensing the ART correctly. They reported that the adherence services they provided were an essential part of patient care:

“… a big part of my job is if I’m noticing it’s [refilled] late and sitting on my shelf, we’re calling them constantly … Say, if you notice a patient’s not being adherent. Keeping in touch with the doctor and letting the doctor know what’s going on, too, so that way you can have that 3-way relationship between pharmacy, physician, and patient.” (pharmacist, white male)

Barriers to Providing or Accepting Adherence Counseling and Support. Participants described many barriers that deter the provision of adherence support services in the pharmacy setting. Patients expressed frustration regarding complicated insurance systems and anxiety about not being able to receive their medications in a timely manner. Additionally, feeling ill, having concerns about the pharmacy’s location, and the presence of drug-seeking or intoxicated pharmacy patrons negatively affected patients’ desire to be at the pharmacy and their openness to receiving adherence counseling and support services:

“And the pharmacies, they don’t have the medications. They say, ‘Can you come back?’ And it is like, ‘No, I can’t come back, I’m sick—that’s why I am at the pharmacy!’ ” (46-year-old white female)

One common barrier to discussing ART adherence with a pharmacist was the lack of privacy in the pharmacy counseling area. None of the patients explicitly mentioned the fear of revealing their HIV-positive status, though pharmacists were sensitive to this concern:

“It’s, like, the whole lobby doesn’t need to know what I’m getting. Just hand me my stuff … I’ll be trying to whisper … and [pharmacists will] be all loud and I’m, like, ‘Oh, god, please just let me get my medication and get out of here.’ ” (undisclosed age, African American female)

“They don’t want anybody in the pharmacy even knowing what they’re taking … Even if everybody wants to remain confidential, it’s very possible that some word could leak out about your HIV status.” (pharmacist, white male)

“I do know that at other pharmacies they had this line where you had to wait, you couldn’t go beyond a certain point in line. And they don’t do that at my pharmacy, and that is one of the things that I don’t like about my pharmacy. People are right behind you.” (undisclosed age, African American male)

“Some patients, they don’t necessarily feel comfortable talking, especially the HIV patients who do come and see me. They don’t necessarily want to talk about their HIV medications openly.” (pharmacist, Asian male)

Pharmacists may unknowingly erect other adherence communication barriers. Some patients perceived pharmacists as unapproachable and too busy to discuss medications or adherence:

“They don’t really talk about too much of anything because they’re usually always too busy … and they don’t have a whole lot of people working. So, you’ve got to try to let them do what they got to do so they don’t mess up on their medications.” (50-year-old white female)

“I think they have a job to do, and I just think they put up
a wall, like, they just got to do their part and get it out to the customer, and I don’t think they become personable like that.” (undisclosed age, African American female)

Pharmacists stated that time stress was a major barrier to discussing medications and adherence with HIV positive patients:

“And given how busy the pharmacy can be, how much time, realistically, on average, can you really spend with a patient just talking to them about their medication? … when it gets really busy, you might have difficult patients who come in and it might sometimes be hard to spend—especially, if you’re the only pharmacist there—to really spend time talking to them.” (pharmacist, white male)

Feeling Known by the Pharmacy Facilitates a Relationship that Allows for More In-depth Adherence Support and Counseling. Patients found it valuable and important for their health when they had a more personal relationship with someone working at the pharmacy. This personal relationship was hallmark by a pharmacy employee recognizing them, acknowledging them, and knowing them by name. Some patients established a connection with a technician or other pharmacy personnel rather than a pharmacist, though patients did not always appear to understand the different roles and responsibilities of pharmacy staff members. The feeling of being known fostered an environment that could facilitate the acceptance of adherence support:

“You can go to some pharmacies and they just say ‘here and send you on your way. I don’t know if it’s the staff or what it is, but it’s like they don’t care. When you get a pharmacist who can relate to you, it gives you a different feeling about yourself and the employees at the pharmacy.” (59-year-old African American male)

“The guy there, he acknowledges you by your name, and when you come in, he’ll say, ‘Hi, Miss Johnson’ or ‘Hi, Miss Jones’ or whoever. And ‘How you doing today? I got your medicine’ or ‘I’m sorry … I’ll call you when it’s ready’ or ‘Do you want to wait?’ … He makes you welcome. You’re like a family, you’re part of that family right there, in that structure.” (58-year-old African American female)

Despite their patients’ perceptions that they were too busy to talk, most pharmacists recognized the value in establishing a more personal relationship to build trust and open the lines of adherence communication:

“I have about 300-plus HIV patients … and I know the majority of them by name. And it’s very difficult to find that in a community setting.” (pharmacist, white male)

“I try to catch people when they’re first here at the pharmacy so that they get my name. They know who the pharmacists are. They know that they’re free to call if they have questions and we’ll help them…. I think that relationship’s vital. It’s been done away with a little bit in the last decade or two in the pharmacy world, but I do think it’s important.” (pharmacist, white male)

Most patients could not recall their pharmacist ever speaking with them about ART adherence. In the few instances a patient did recall their pharmacist asking about ART adherence, they responded positively:

“It makes me feel good, it really does. ’Cause that lets me know there is somebody out there besides family, somebody that I really don’t know, but just that he’s my pharmacist and he shows me and lets me know that he cares.” (undisclosed age, African American female)

“Well, they really don’t say nothing to me, just ‘How are you doing, how you feeling? Have you been taking your meds every day?’ ‘Yeah, I take it.’ … It’s very important ‘cause that lets me know that they care and that they’re not just, ‘Here, take your medicine, go on about your business.’” (46-year-old African American female)

A Need for Training in Effective Adherence Communication. Pharmacists suggested that additional training would improve patient-pharmacist relations, which could, in turn, facilitate the provision of adherence counseling and support. Patients were more concerned that pharmacists were adequately trained to fill medications correctly and that there was adequate staff available to serve the patients, though they did not suggest that additional staff would allow for more one-on-one counseling time or adherence support with a pharmacist:

“If there could be a way that the people who are doing this sort of work—more intensive work dealing with patients—could be somehow better trained or somehow more able to deal with patients, [that would be helpful].” (pharmacist, white male)

“I guess maybe there’s a certain kind of skill set of certain things that we would be able to learn to say to them, to drive the point home. Or maybe some kind of a script that would give us a guideline of, okay, here are the things that you want to say to people and what not to say to people.” (pharmacist, white female)

Discussion

Although various quantitative studies support the effectiveness of pharmacies providing ART adherence support, there remains a wide variation in the adherence interventions provided and little guidance on how new pharmacies might begin to offer enhanced HIV services.1-4,6 Gaining a baseline understanding of how ART adherence counseling and support is currently provided in U.S. community pharmacies can help
to guide the development of feasible interventions that can be replicated in other pharmacies. Adherence support techniques described by pharmacists in our San Francisco-based study are similar to those described in another qualitative study: adherence counseling, medication education, telephone reminders to encourage timeliness of prescription refills, and collaboration with treating clinicians.\textsuperscript{11} The barriers to providing ART adherence support reported in our study were similar to those found in 2 qualitative studies, particularly around job time stress and desires for additional training.\textsuperscript{11,12} Our data is consistent with this published literature, and our study also adds valuable insight from the patient’s perspective because ART adherence support that is provided by pharmacists may be interpreted differently by their patients.

For pharmacies that are striving to create services for HIV-positive patients, our study highlights several factors that might be considered. Patients in our study appreciated the challenges pharmacists face associated with dispensing, but they otherwise had low expectations with regard to pharmacists providing adherence support. This means that pharmacies may need to invest more time to promote and expound on the personal health benefits of patients engaging in their ART adherence support and counseling services. Our study also suggests that because patients value a personal connection prior to engaging in ART adherence support, blanket approaches to promote adherence services may not be as effective as one-on-one outreach even though large promotional campaigns are certainly more efficient. Patients may be wary of accepting even the best pharmacy services if they are offered by someone with whom they have not established a strong familiarity. Pharmacists can fully engage in treatment advocacy for HIV-positive patients if they are able to create positive expectations and effectively encourage patients to accept adherence services.\textsuperscript{13}

Once clients are engaged, pharmacies must consider what adherence support techniques they will employ. Studies suggest that adherence support should be tailored to the individual, and pharmacies must decide on the suite of interventions they will provide, based on their capacity. Pharmacists in our study were more confident providing adherence reminder devices such as bubble packing and refill services such as reminders and home delivery. Pharmacists appeared less confident regarding their effectiveness in adherence counseling. Because patients in our study did not often recall their pharmacists asking about adherence, it appears that pharmacists should increase the frequency with which they assess ART adherence. When pharmacy practices dictate counseling only on new prescriptions, this creates missed opportunities to intervene on adherence at each refill. Forgetting and practical barriers certainly play a role in poor adherence, yet pharmacists counsel-

ing efforts should strive to influence more complex adherence issues such as motivation. Additional training in communication, health behavior change, and counseling techniques such as motivational interviewing may increase pharmacist confidence in addressing more challenging adherence cases.\textsuperscript{14}

Lastly, our study highlights several additional general opportunities to enhance community pharmacy ART adherence support. Workflow issues such as creating private spaces for counseling and having adequate staff to fulfill dispensing duties may enhance patient engagement in adherence support. Pharmacists are also in a unique position to facilitate referrals, for example, to mental health programs, clinics, substance abuse programs, and other services that can greatly aid ART adherence. Developing relationships with relevant HIV/AIDS community-based organizations and providers can also serve to solidify the pharmacist’s role on the adherence health care team. These changes are important steps to shift the role of community pharmacists from medication dispensers to treatment advocates who improve the effectiveness of HIV therapy.

Limitations
One limitation to our study was that participants were recruited from San Francisco. Opinions and experiences may not be generalizable to other HIV populations and pharmacy practices. We enrolled a limited number of patients and pharmacists, though this was dictated by data saturation. Pharmacists in our study provided care for a high-volume of HIV-infected patients, so although the sample was small, we believe that it captured a reasonable range of ART adherence support techniques that pharmacists might employ. Patients in our study may not have interacted with the pharmacists that we interviewed, but it is likely that they interacted with other pharmacists working at the same locations. Lastly, we did not measure adherence, so it is unclear if our sample was reflective of a highly adherent population that did not need adherence counseling and therefore did not either request or receive it from their pharmacists.

Conclusion
Pharmacists support ART adherence using a variety of techniques that range from counseling to medication synchronization to use of technology to remind patients to pick up refills. Pharmacies developing HIV specialty services should consider increasing promotion of the benefit of engaging in adherence support, increasing training to improve communication in the pharmacist-patient relationship, and facilitating work spaces that support adherence counseling. These practices and others are important steps to enhance the role of pharmacists as adherence counselors and treatment advocates.
A Qualitative Study Examining HIV Antiretroviral Adherence Counseling and Support in Community Pharmacies

Authors

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DISCLOSURES

This research was funded by grants from the National Institute of Mental Health, which were obtained by Cocohoba and Johnson. Cocohoba reports that she has also received a grant from Gilead Sciences and travel honoraria unrelated to this research. Comfort reports that she has a grant pending from the National Institutes of Health, is a consultant for The Bridging Group, and has received royalties from the University of Chicago Press and honoraria and travel expenses unrelated to this research. Kianfar reports no conflicts of interest relating to this research. Johnson reports that she has grants pending from NIH, is a member of the Data Safety Monitoring Board for Partners Health, and serves as a consultant for the AIDS Foundation of Chicago, all unrelated to this research.

Study concept and design were contributed primarily by Cocohoba, with assistance from Comfort and input from Johnson and Kianfar. Cocohoba had primary responsibility for data collection, with assistance from Kianfar; data interpretation was the work of Cocohoba, with assistance from Kianfar and input from Comfort and Johnson. The manuscript was written primarily by Cocohoba, with assistance from Comfort and Johnson and was revised primarily by Cocohoba with assistance from Johnson.

REFERENCES


## APPENDIX  Semistructured Interview Guide (Online Reference)

### Questions for Patients

1. How long have you lived in the Bay Area?
2. As I explained before, we’re interested in learning more about how people use pharmacies. Can you tell me about how you decided to go to the pharmacy that you currently use?
   a. Prompts: How long have you been using it? What about this pharmacy made you choose it? How often do you go there?
3. Can you describe the personalities of the pharmacists that work at the pharmacy?
4. What kind of things does the pharmacist talk to you about when discussing your HIV medicines? Can you give some examples of things they might say to you?
   a. Prompts: What did you talk about with your pharmacist the last time you went to the pharmacy? How about the time before that? How much time does the pharmacist usually spend talking to you? Would you prefer to spend more, or less, time talking with the pharmacist? How do you usually feel emotionally after talking with the pharmacist?
5. How often does the pharmacist give you information on your HIV medications?
   a. Prompts: How important is it to you that the pharmacist talks to you about your HIV medicines?
6. Sometimes pharmacists remind patients to take their medicines every day. Sometimes they try other ways to help patients take their medicines every day. Has your pharmacist ever tried to help you take your HIV medicines regularly?
   a. Prompts: What exactly did they say or do for you? Give me an example. Was this helpful? [If yes] Tell me about what was helpful to you. [If no] Tell me about what was not helpful to you.
7. Does your pharmacist think it’s important to remind you to take your HIV medicines regularly? What makes you think this?
8. What do you think might help pharmacists talk to their patients? What gets in the way of pharmacists talking to their patients?
   a. Prompt: What’s the most difficult thing about talking to your pharmacist? How comfortable or uncomfortable are you talking to your pharmacist about missing your medicines? What makes you feel this way?
9. How can pharmacists help patients take their medicines better?
   a. Prompt: What would you like to have your pharmacist discuss with you?
10. Most people only see their pharmacist at the pharmacy. How would you feel if your pharmacy called you to see how you were doing with your medicines?
11. How much (if at all) does your pharmacist influence the way you take your medicines?
12. This has been really helpful and interesting. I don’t have any more questions for you, but is there anything I left out that you would like to share with me?

### Questions for Pharmacists

1. How long have you been a pharmacist?
   a. Prompts: Where did you go to pharmacy school? What made you choose pharmacy as a career? What kinds of jobs have you had as a pharmacist?
2. Tell me a little bit about your pharmacy work environment
   a. Prompts: How long have you been working there? How many patients do you serve? Would you describe it as slow, moderate, or busy?
3. Can you describe the patients that come to the pharmacy?
4. How important do you think it is to counsel patients on their medicines?
   a. Prompts: How often do you counsel HIV positive patients on their medications? Do your patients feel it’s valuable for you to counsel them? How much time do you spend talking to the average patient? Under what circumstances do you spend more time talking to a patient?
5. What kinds of things do you talk about when discussing HIV antiretroviral medicines with a patient?
   a. Prompts: Can you give some examples? What if you picked any antiretroviral medication. If I was one of your patients how would you counsel me on this? What is your impression of how patients receive this information from you?
6. When was the last time you counseled a patient on adherence?
   a. Prompts: Is this something you do regularly? Why, or why not?
7. How do you (or how would you) counsel a patient on adhering to their antiretroviral medicines?
   a. Prompts: What do you say/what would you say? Can you recount some instances when you’ve counseled a patient on adherence at your pharmacy? What happened?
8. What might help you counsel your patients better?
   a. Prompt: What gets in the way of talking to your patients? What’s the most difficult thing about talking to your patients? What’s the most difficult thing about talking to your patients about adherence?
9. How do you think pharmacists can help patients take their medicines better?
10. How comfortable would you be calling patients who appear to be missing their medications? Do you think this is a good strategy to assess and help patients with poor adherence? If yes, why? If no, why not, or what would be a good strategy?
11. How much of an impact do you think you have on your patients’ medication-taking behavior?
12. This has been very helpful and interesting. These are all the questions I have for you, but is there anything I left out that you would like to share with me?
Medical Costs Associated with Use of Systemic Therapy in Adults with Colorectal Cancer

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ABSTRACT

BACKGROUND: New cytotoxic agents and regimens, as well as immunotherapeutics, have recently been introduced for treatment of colorectal cancer (CRC).

OBJECTIVE: To identify the patient-related and clinical and treatment-related factors associated with higher total health care expenditures in newly diagnosed patients with CRC who are receiving systemic therapy (biologic or chemotherapy) from a commercially insured population.

METHODS: A longitudinal, retrospective analysis was employed to estimate costs and determinants of CRC treatment in a U.S. claims database for health care services used by commercial patients aged 18 to 64 years, who were diagnosed with CRC between January 1, 2005, and June 30, 2009. Generalized linear regression modeling was used to estimate the influence of demographic, clinical, and treatment factors on medical expenditures.

RESULTS: Among the 5,160 patients newly diagnosed with CRC, 99.6% of patients had chemotherapy; 32.6% had biologics; and 85.6% had other pharmaceuticals (excluding the chemotherapy and biologics of interest). The average annualized per patient cost of CRC treatment was $97,400 and consisted of chemotherapy ($17,500), biologics ($30,400), other pharmaceuticals ($2,300), inpatient treatment ($26,300), and outpatient treatment ($42,900).

CONCLUSION: The health care cost of CRC treatment is increasing significantly over time, which is most likely caused by the use of new regimens, higher chances of surgery and radiation, and occurrence of various comorbidities and metastatic diseases due to increasing survival time.


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What this study adds

- Previous studies have demonstrated that new CRC regimens could have higher costs; however, little is known about the trend of medical costs over time and the impact due to health care inflation and other confounding factors. Our study adds an economic assessment of comparative costs and cost-effectiveness, as they are important for assessing the value of treatment regimens for CRC.

- Our findings have demonstrated that health care costs of CRC treatment is increasing significantly over time.

Colorectal cancer (CRC) is among the most common malignancies in developed countries. In 2008, it was estimated that there were 1,233,000 incident cases of CRC diagnosed worldwide: 663,000 new cases diagnosed in men and 570,000 new cases in women, and almost 60% of the cases occurred in developed regions. Additionally, the medical costs associated with the diagnosis and treatment of CRC patients are substantial, which undoubtedly has become a significant economic burden on the countries and the families with CRC patients. Compared with matched patients with no cancer, total monthly costs were $14,585 higher for metastatic CRC patients, which was driven by higher inpatient ($7,546) and outpatient ($6,749) care. Furthermore, with the development of pharmaceuticals and medical technology, infusing new chemotherapies and biologics, CRC therapies could further increase the cost burden on the health system.

New cytotoxic agents and regimens, as well as immunotherapeutics, have been introduced during the past 8 years. Clinical studies indicate that bevacizumab in combination with 5-fluorouracil/leucovorin (FU/LV) and bevacizumab in combination with irinotecan plus FU/LV (Folfiri) are clinically more effective in comparison with standard chemotherapy options for the first-line treatment of metastatic CRC. However, these expanded options have increased treatment costs and, in some cases, toxicity. As an example, an assessment of 8 commonly prescribed regimens reported that the largest cost differential for 6 cycles of planned treatment was $35,971, between Folfiri ($36,999) and FU/LV ($1,028). A study in Greece illustrated that the mean 20-week total cost varied between €18,242 and €19,701 per patent for using cetuximab. Although previous studies have demonstrated that new CRC regimens could have...
Medical Costs Associated with Use of Systemic Therapy in Adults with Colorectal Cancer

higher costs, little is known about the trend of medical costs over time and the impact due to health care inflation and other confounding factors. Therefore, economic assessment of comparative costs and cost-effectiveness are important for assessing the value of treatment regimens for CRC. The aim of this study was to identify the patient-related and clinical and treatment-related factors associated with higher total health care expenditures in newly diagnosed patients with CRC who are receiving systemic therapy (biologic or chemotherapy) from a commercially insured population.

Methods
Data Source
A retrospective analysis was performed using enrollment, medical, and pharmacy claims data from the MarketScan Commercial and claims encounter database (Truven Health Analytics). The MarketScan database provides anonymous paid claims data for individual patients covered by commercial health plans that represent several different kinds of employers in the United States and approximately 18 to 20 million commercial lives annually. The database records annual prevalence, cost, demographic, clinical, and utilization statistics for health conditions by type of insurance coverage. Health care services utilized by newly diagnosed patients between January 1, 2005, and June 30, 2009, were included in this analysis. Eligible patients satisfied the following requirements: (a) aged 18 to 64 years when newly diagnosed with CRC and (b) at least 6 months of patient history prior to CRC diagnosis and at least 1-year post-index continuous enrollment.

Inclusion and Exclusion Criteria
Patients newly diagnosed between January 1, 2005, and June 30, 2009, with malignant neoplasm of colon (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] diagnosis code 153) or malignant neoplasm of rectum, rectosigmoid junction, and anus (ICD-9-CM diagnosis code 154) and having evidence of 1 of the selected treatments (oxaliplatin, irinotecan, fluorouracil [FU], leucovorin [LV], capcitabine, bevacizumab [Avastin] cetuximab, and panitumumab) were identified. As depicted in Figure 1 and Figure 2, our study utilized a look-back period of 180 days to establish whether patients had prior evidence of CRC. Diagnosis of CRC is termed the “index event” for this analysis. Patients with at least 6 months of patient history prior to and at least 1 year of continuous enrollment post-index event were included in the analysis. Patients who had a diagnosis of or treatment for cancer in the 6 months prior to CRC diagnosis and patients who were not continuously enrolled with pharmacy benefits were excluded. Also, we removed patients aged either over 64 or less than 18 years at diagnosis and deleted information when the exact age at the end of the study was more than aged 65 years.

Patients were followed from initial CRC diagnosis (index date) to disenrollment or June 30, 2010 (Figure 2). Chemotherapy and biologic treatments over time were analyzed to identify lines of therapy. Total health care costs, including costs associated with CRC and other comorbidities, were calculated.
**TABLE 1** Patient Demographics and Comorbidities at Diagnosis

<table>
<thead>
<tr>
<th>Item</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18-50 years</td>
<td>1,618</td>
<td>31.4</td>
</tr>
<tr>
<td>51-60 years</td>
<td>2,608</td>
<td>52.3</td>
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<tr>
<td>61-64 years</td>
<td>844</td>
<td>16.4</td>
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<tr>
<td><strong>Gender</strong></td>
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<td></td>
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<tr>
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<td>2,822</td>
<td>54.7</td>
</tr>
<tr>
<td>Female</td>
<td>2,338</td>
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</tr>
<tr>
<td><strong>Metastasis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>2,102</td>
<td>40.7</td>
</tr>
<tr>
<td>Yes</td>
<td>3,058</td>
<td>59.3</td>
</tr>
<tr>
<td><strong>Comorbidities</strong></td>
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<td></td>
</tr>
<tr>
<td>All*</td>
<td>1,113</td>
<td>21.6</td>
</tr>
<tr>
<td>Diabetes</td>
<td>654</td>
<td>12.7</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>238</td>
<td>4.6</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>76</td>
<td>1.5</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>68</td>
<td>1.3</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>46</td>
<td>0.9</td>
</tr>
<tr>
<td>Chronic renal failure</td>
<td>31</td>
<td>0.6</td>
</tr>
</tbody>
</table>

*All comorbidities included myocardial infarction, dementia, paralysis, various cirrhoses, moderate-severe liver disease, ulcers, rheum (including rheumatoid arthritis, systemic lupus, mixed connective tissue disorder, polymyositis, rheumatic polymyositis), malignant cancer, metastatic cancer, autoimmune deficiency syndrome, and the 6 listed in this table.

**Lines of Therapy**

The daily chemotherapy and/or biologic use profile was examined to define each treatment regimen and lines of therapy by temporal relationship and sequencing of treatment regimens. First-line therapy was defined as all chemotherapy and/or biologic drugs given to a patient during the first 36 days after initiation of treatment and administered for 1 or more cycles. Discontinuation of single drug from a combination regimen was not considered a change in line of therapy. The addition or substitution of chemotherapy or a biologic agent was considered a new line of therapy. Systemic chemotherapy and biologic treatments were analyzed over time to identify lines of therapy. This included the following products: oxaliplatin, irinotecan, FU, LV, capcitabine, bevacizumab [Avastin], cetuximab, and panitumumab.

**Statistical Analyses**

The medical costs of CRC treatment consisted of chemotherapy, biologics, other pharmaceuticals, inpatient, and outpatient. Other pharmaceuticals excluded the chemotherapy and biologics of interest. Inpatient expenditure included other related costs except chemotherapy, biologics, and surgery. Outpatient expenditure included surgery, office visit, hospital, emergency room, and other related costs.

**TABLE 2** Lines of Systemic Treatment for Colorectal Cancer Patients

<table>
<thead>
<tr>
<th>Agent</th>
<th>First Line Only (N = 2,306)</th>
<th>First and Second Lines Only (N = 1,825)</th>
<th>Third + Lines (N = 1,029)</th>
<th>Chi-square</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Yes</td>
<td>2,292</td>
<td>1,817</td>
<td>1,028</td>
<td>4.2</td>
<td>0.124</td>
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<tr>
<td>No</td>
<td>14</td>
<td>8</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biologics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>281</td>
<td>539</td>
<td>864</td>
<td>1,679.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No</td>
<td>2,025</td>
<td>1,286</td>
<td>165</td>
<td></td>
<td></td>
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</tbody>
</table>

All statistics were computed using SAS 9.2 (SAS Institute Inc., Cary, NC). Descriptive statistics included mean, frequency, and percentage. The chi-square test was employed to examine the distribution of chemotherapy and biologics across patients who received first line only, first and second lines only, and third + lines of treatment (the two-sided P value was set at 0.05). The excess expenditures associated with additional lines of therapy were estimated as the difference between the total medical expenditures for those with first line of therapy versus second and third + lines of therapy. Generalized linear regression modeling (with gamma distribution and log link function) was used to estimate the influence of demographic, clinical, and treatment factors on medical expenditures (the variables with P<0.05 were considered as statistically significant factors). We also used nonlinear regression modeling to fit the trend of treatment costs for CRC patients from 2005 to 2009 in order to examine whether the costs increased over time after adjusting for health care inflation.

**Results**

A total of 5,160 subjects diagnosed with CRC were included in the analysis. The profiles of patients in this study are shown in Table 1.

**Treatments**

Among the patients newly diagnosed with CRC, all patients received either chemotherapy or biologics: 32.6% (1,684 of 5,160) received biologics, and 85.6% (4,417 of 5,160) had other pharmaceuticals (excluding the chemotherapy and biologics of interest). Of these patients, 44.7% (2,306 of 5,160) received first line only; 35.4% (1,825 of 5,160) received first and second lines only, and 19.9% (1,029 of 5,160) received third + lines of treatment for CRC. Table 2 shows that regardless of what therapy line was selected, chemotherapy was most likely used to treat CRC patients. However, biologics were more commonly added into regimens in the third + lines (84.0%) compared with the first line only (12.2%) and the first and second lines only (29.5%).
Also, 59.3% (3,058 of 5,160) of patients were found with metastatic diseases when they were diagnosed with CRC. Patients with metastatic diseases were more likely to have chemotherapy combined with biologics (50.6% vs. 6.5%) compared with those without metastasis ($\chi^2 = 1,100; P < 0.01$). In addition, all patients received some form of outpatient care, and more than 95% were admitted as inpatients.

### Medical Costs

The average annualized cost of CRC treatment per patient was $97,400, including chemotherapy ($17,500), biologics ($30,400), other pharmacy ($2,300), inpatient treatment ($26,300), and outpatient treatment ($42,900). The total costs were significantly increased from first line only ($70,500), first and second lines only ($100,100), to third+ lines ($152,900). Outpatient expenditure (including surgery, office visit, hospital, and emergency room) was the leading cost for CRC treatment at each treatment line (see Table 3).

We also compared the treatment cost of CRC patients with and without metastasis. The results indicated that the average annualized cost for patients with metastasis was nearly twice that of those without metastasis ($121,800 vs. $61,800, t = 29.5, P < 0.01$), and the distribution of cost components was similar to those mentioned above (Table 4).

#### Cost Trend Over Time

From 2005 to 2009, the annualized health care inflation rate in the United States varied between 3.17% and 4.42%. In order to examine whether the medical cost of CRC treatment increased over time after adjusting for health care inflation, we conducted the following analysis and found that after adjusting for health care inflation, the average treatment cost of a CRC patient increased significantly from $29,701 to $51,397. Figure 3 depicts the trend of medical costs over time as demonstrated by an exponent distribution ($F = 415.58; P < 0.01$) as follows:

$$\text{Cost} = e^{(0.0312 \times \text{year} - 2004)}$$

Cost is the inflation adjusted cost for CRC treatment, and year is from 2005 to 2009. As seen in Figure 3, medical costs trended upwards over time (increased by 17.6% annually) even when health care inflation had been adjusted. The question remains: What were the reasons behind the macro level of costs increasing? To address this question, our study analyzed the determinants of cost.

#### Determinants of Cost

Generalized linear regression modeling (GLM) was employed to estimate the influence of therapy lines and demographic/clinical covariates on medical expenditures for CRC treatment (Table 5). We found that patients receiving...
Folfiri did not have higher costs; in fact, they had lower costs than those receiving FOLFOX (FU/LV + oxaliplatin) or FU. However, patients receiving FolfoxA (FOLFOX + bevacizumab) or FolfiriA (Folfiri + bevacizumab) or bevacizumab alone had higher costs for CRC treatment. CRC patients with post-index metastasis had higher total costs. CRC patients aged 61 to 64 years had lower medical expenditures than those patients aged 18 to 50 years, but the cost difference was not significant between patients aged 51 to 60 years and those aged 18 to 50 years. Patients from the Northeast, North central, and West regions had higher costs than those from other areas of the United States. As compared with 2005, the average costs in 2006 were higher but not in 2007, 2008, and 2009. Male patients cost more than female patients. Patients having comprehensive insurance plans (health maintenance organizations and indemnity insurance plans) had lower costs than those having preferred provider organization insurance plans. The patients who waited less than 30 days between diagnosis and treatment had higher costs than those within 30-59 days. Other factors associated with higher cost included post-index surgery, post-index radiation and comorbidities (Charlson Comorbidity Index). In addition, we found that a number of factors were not associated with higher costs of CRC treatment, such as pre-index metastatic diseases and index colon cancer (vs. rectal cancer).

Discussion

This study comprehensively analyzed medical costs associated with the use of chemotherapy and biologics among adults with CRC using a nationwide database. Our study found that the health care costs of CRC treatment have increased significantly over time, which is most likely attributable to the use of a new drug regimen, increased use of surgery and radiation, and the occurrence of various comorbidities and metastatic diseases.

Undoubtedly, the development of new CRC treatments has brought significant benefits to patients. From the late 1980s to the early twenty-first century, the 5-year survival rate of CRC in Europe increased by approximately 20%; for example, in Switzerland, it increased from 49.5% to 65.3%. Furthermore, the 5-year survival rate of CRC was higher in the United States than in Europe. Until recently, 3 regimens dominated first-line treatment of CRC. FU, available since the 1960s, which has been routinely administered with FU/LV since the early 1990s or with irinotecan (IFL or Folfiri) since 2000. In the past decade, the U.S. Food and Drug Administration approved several new drugs, such as capecitabine, oxaliplatin, bevacizumab, cetuximab, and panitumumab, which have been widely used in the treatment of CRC patients. This study found that biologics, including bevacizumab, cetuximab, and panitumumab, were more likely added into regimens in the third+ lines as compared with earlier lines.

The health care costs of CRC patients, however, increased with the use of these new treatments. This study found the average annualized cost of CRC treatment per patient was $97,400, and it increased significantly from the first line only to the third + lines. Furthermore, we must also consider the effect of immortal time bias (immortal time refers to a span of time in the observation or follow-up period of a cohort during which the outcome under study could not have occurred). Our study findings were based on an assumption that all CRC patients could survive from first line to third + lines. We did not factor in those patients who died before entering the late-stage treatment cohorts who may have had a worse prognosis requiring that they pay more for treatment. Hence, the cost of CRC treatment at late lines may very well have been more expensive.

This study also found that patients with post-index metastasis had higher costs than those with no metastasis due to higher expenditure on outpatient costs, biologics, inpatient, and chemotherapy. The increase in biologic and chemotherapy treatment costs could mainly be attributed to the high price of “new drugs.” Patients receiving FolfoxA, FolfiriA, or bevacizumab alone had significantly higher costs for CRC treatment. Recently, the “new drugs” have been widely used to treat CRC patients in developed countries, which is why CRC patients in developed countries have higher costs for survival. It was estimated that CRC patients may pay approximately $3,000 per dose in order to get 6 months of survival.
TABLE 5  Determinants of Colorectal Cancer Treatment Costsa

<table>
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<tr>
<th>Factors</th>
<th>Groups</th>
<th>Estimate</th>
<th>Standard Error</th>
<th>Wald Chi-square</th>
<th>P Value</th>
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<td>0.021</td>
<td>3.50</td>
<td>0.059</td>
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<tr>
<td></td>
<td>61-64/18-50</td>
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<td>0.029</td>
<td>8.87</td>
<td>0.003</td>
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<tr>
<td>Sex</td>
<td>Male/female</td>
<td>0.078</td>
<td>0.019</td>
<td>17.22</td>
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<tr>
<td>Year</td>
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<td>0.031</td>
<td>7.66</td>
<td>0.006</td>
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<tr>
<td></td>
<td>2007/2005</td>
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<td>0.00</td>
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<td>2008/2005</td>
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<td>0.033</td>
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<tr>
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<td>0.043</td>
<td>2.35</td>
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<td>0.022</td>
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<td>0.029</td>
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<td>Insurance plan</td>
<td>Comprehensive/PPO</td>
<td>-0.087</td>
<td>0.035</td>
<td>6.07</td>
<td>0.014</td>
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<tr>
<td></td>
<td>Others/PPO</td>
<td>0.103</td>
<td>0.045</td>
<td>5.25</td>
<td>0.022</td>
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<td></td>
<td>Point of service/PPO</td>
<td>0.048</td>
<td>0.028</td>
<td>2.97</td>
<td>0.085</td>
</tr>
<tr>
<td>Charlson Comorbidity Score</td>
<td>1/0</td>
<td>0.075</td>
<td>0.026</td>
<td>8.67</td>
<td>0.003</td>
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<td>2/0</td>
<td>0.108</td>
<td>0.049</td>
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<tr>
<td></td>
<td>3+/0</td>
<td>0.347</td>
<td>0.080</td>
<td>19.03</td>
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<tr>
<td>Post-index metastasis</td>
<td>Yes/No</td>
<td>0.622</td>
<td>0.020</td>
<td>969.80</td>
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<tr>
<td>Pre-index surgery</td>
<td>Yes/No</td>
<td>-0.056</td>
<td>0.020</td>
<td>7.76</td>
<td>0.005</td>
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<td>Post-index surgery</td>
<td>Yes/No</td>
<td>0.261</td>
<td>0.032</td>
<td>67.6</td>
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<tr>
<td>Post-index radiation</td>
<td>Yes/No</td>
<td>0.170</td>
<td>0.025</td>
<td>46.59</td>
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<td>Follow-up days</td>
<td>Less than 30/30-59</td>
<td>2.0E-4</td>
<td>1.0E-5</td>
<td>34.83</td>
<td>&lt;0.001</td>
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<td>60-89/30-59</td>
<td>0.061</td>
<td>0.028</td>
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<td>0.025</td>
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<td>0.026</td>
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<td>Folfiri4</td>
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<td>0.343</td>
<td>0.034</td>
<td>99.66</td>
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<tr>
<td>Bevacizumab alone</td>
<td>Yes/No</td>
<td>0.355</td>
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<td>5-Fluorouracil</td>
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<td>5-Fluorouracil</td>
<td>Yes/No</td>
<td>-0.176</td>
<td>0.031</td>
<td>32.91</td>
<td>&lt;0.001</td>
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</tbody>
</table>

*aOther factors with P > 0.05 included pre-index metastatic diseases, index colon cancer (vs. rectal cancer), and Folfiri (FU/LV plus irinotecan).
*bFOLFOX is FU/LV (fluorouracil/leucovorin) plus oxaliplatin.
*cFolfox is FOLFOX plus bevacizumab.
*dFolfin/4 is FOLFOX plus irinotecan plus bevacizumab.

This study indicated that the annualized total cost of care in newly diagnosed CRC patients increased by 17.6% annually from 2005 to 2009. The dominant reason may be the development of new regimens over time, as new drugs for CRC treatment were created and integrated into the systemic therapy with higher prices in the market. Additionally, more examinations and surgeries using modern technology were implemented over the time period studied. Other relevant factors could also affect the change of treatment costs for CRC patients simultaneously. Insured compared with uninsured participants were significantly more likely to have ever completed CRC screening.17 The CRC patients with noncomprehensive insurance plans could have higher medical costs. Patients who waited less than 30 days between diagnosis and treatment cost more than those who waited between 30-59 days, which could be interpreted that the patients who received their treatments earlier were sicker so that they had higher costs. Also, the cost change could be associated with the age-specified ratios of CRC patients, which has been an increasing trend among the younger population since 2004.18 Additionally, CRC patients often have diverse comorbidities, which could lead to a similar increasing trend of treatment costs in recent years.

Limitations
There are several limitations that should be considered when interpreting this work. First, the study sample was restricted to CRC patients aged 18 to 64 years (working age) and did not include retired/older patients. Medical costs of CRC treatment among older patients could be different from the younger population.19 In addition, a potential selection bias should also be recognized because this study used only the MarketScan claims database, which focused on the patients aged 18 to 64 years covered by commercial health plans. Hence, one should exercise caution in extrapolating the results of this study to
other populations with CRC, especially for the elderly population (over 65 years old). There are several other potential limitations with this study because of the claims data-based methodology. First, CRC was identified using ICD-9-CM codes and did not include information on patients based upon diagnostic tests. Second, to identify the cohorts, it was assumed that ICD-9-CM diagnosis codes were complete and accurate. Third, the database included only ICD-9-CM diagnosis codes that were reported with successfully reimbursed medical and pharmacy claims. Fourth, race/ethnicity, smoking status, and all of the other noncoded information (e.g., laboratory results) were not captured in this database. Fifth, this study also had limitations in classifying patients according to treatment line and describing instances where the algorithm could have failed in tracking a switch from one treatment line to another. Another limitation is the scope of generalizability of the study results. Treatments may have been influenced by the different formulary status of the treatments in the health plans. It is likely that treatments had similar accessibility to patients and prescribers.

## Conclusion

Based on current evidence, randomized, prospective studies are needed in the future to confirm and disseminate the findings of clinical benefits of the new regimens in managing CRC.

### DISCLOSURES

Bayer HealthCare Pharmaceuticals Inc. funded this study. Asche was paid as a consultant as were Sullivan, Ramsey, Shermock, and Sarma. Ren is an employee of the University of Illinois College of Medicine, and Seal, Kreilick, Foltz Boklage, and Valluri are paid employees of Bayer HealthCare Pharmaceuticals Inc.

Study concept and design were contributed by Seal, Shermock, and Valluri, with assistance from Sullivan, Ramsey, Kreilick, Sarma, and Asche. Data were collected by Kreilick, Foltz Boklage, and Sarma, with assistance from Seal, Shermock, and Ren. Data interpretation was primarily the work of Sullivan, Ramsey, Seal, Shermock, and Valluri, with assistance from Kreilick, Foltz Boklage, Sarma, and Asche. The manuscript was written by Ren, Valluri, and Asche, with help from Seal, Sullivan, Ramsey, and Shermock. The manuscript was revised by Sullivan, Ramsey, Seal, and Asche, with help from Ren and Valluri.

### REFERENCES


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Identifying Patient Characteristics Associated with High Schizophrenia-Related Direct Medical Costs in Community-Dwelling Patients

Pooja R. Desai, MS; Kenneth A. Lawson, PhD; Jamie C. Barner, PhD; and Karen L. Rascati, PhD

ABSTRACT

BACKGROUND: Schizophrenia is a chronic, debilitating disease that affects approximately 1% of the U.S. population and has disproportionately high costs. Several factors, including age, gender, insurance status, and comorbid conditions, have been hypothesized to be associated with schizophrenia-related costs.

OBJECTIVE: To identify demographic and clinical characteristics of community-dwelling schizophrenia patients experiencing high schizophrenia-related direct medical costs.

METHODS: Community-dwelling patients with a diagnosis for schizophrenic disorder (ICD-9-CM code 295) and other nonorganic psychoses (ICD-9-CM code 298) were identified from the 2005-2008 Medical Expenditure Panel Survey (MEPS). Schizophrenia-related direct medical costs were calculated for (a) inpatient hospitalizations; (b) prescription medications; and (c) outpatient, office-based physician, emergency room, and home health care visits. Using Andersen’s Behavioral Model of Health Services Use and the literature, factors that could potentially affect schizophrenia-related direct medical costs were identified. Based on the distribution of their mean annual costs, patients were classified into high- and low-cost groups. Logistic regression was used to determine the likelihood of high-cost group membership based on age, sex, race, insurance status, marital status, region of residence, family income as a percentage of poverty line, number of medical comorbidities, number of mental health-related comorbidities, patient-perceived general health status, patient-perceived mental health status, and year of inclusion in MEPS. In addition, a generalized linear model (GLM) regression (gamma distribution with a log-link function) was used to evaluate the relationships between the independent variables and total schizophrenia-related direct medical costs as a continuous variable.

RESULTS: From the MEPS database, we identified 317 patients with schizophrenia who represented 2.75 million noninstitutionalized, community-dwelling schizophrenia patients in the United States between 2005 and 2008. The logistic regression procedure showed that older patients (OR = 0.933, 95% CI = 0.902-0.966) and patients with a spouse (OR = 0.150, 95% CI = 0.041-0.555) were less likely to be in the high-cost group, while those who reported having “poor” perceived general health status (OR = 15.548, 95% CI = 1.278-189.127) were more likely to be in the high-cost group. The GLM regression procedure showed that younger patients (compared with older patients), African Americans (compared with Caucasians), patients with private insurance (compared with the uninsured), and those living in the northeastern United States (compared with those living in the southern United States) had higher schizophrenia-related direct medical costs.

CONCLUSION: Identification of factors associated with a high-cost population may help decision makers in managed care, government, and other organizations allocate resources more efficiently and health care providers manage patients more effectively through assignment of these patients to case managers and appropriate monitoring and treatment.


What is already known about this subject

• Schizophrenia is a debilitating disease that exerts a high financial burden on society.
• A study using the Medical Expenditure Panel Survey (McDonald 2005) has indicated that a small percentage of community-dwellers with schizophrenia are responsible for a disproportionate amount of associated costs.
• Factors such as early onset of disease, presence of comorbid conditions, hospitalizations, need for outpatient and emergency department visits, need for maintenance medications for long periods, and need for informal care have been hypothesized to be responsible for the high costs of schizophrenia.

What this study adds

• This study used a combination of the Behavioral Model of Health Services Use and the literature to identify potential factors that might influence schizophrenia-related direct medical costs for community-dwelling individuals.
• The logistic regression procedure showed that after controlling for covariates, older patients and married patients were more likely to have lower costs, and those who reported having a “poor” perceived general health status were more likely to have higher costs.
• The generalized linear model regression procedure showed that younger patients (compared with older patients), African Americans (compared with Caucasians), patients with private insurance (compared with the uninsured), and those living in the northeastern United States (compared with those living in the southern United States) were associated with higher schizophrenia-related direct medical costs.

Schizophrenia is a chronic, debilitating illness that is characterized by disturbances of language, perception, thinking, social activity, behavior, and decision-making skills. Several epidemiologic surveys have been conducted to estimate the prevalence of schizophrenia, such as the Epidemiologic Catchment Area study and the National Comorbidity Survey. These studies estimated the overall prevalence of schizophrenia in the United States to be between 0.3% and 1.6% of the population.
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Several studies also have been conducted to estimate the cost of schizophrenia in the United States. The costs associated with schizophrenia have shown a steady rise in the past few decades. Gunderson and Mosher’s (1975) estimate for the total cost of schizophrenia in 1971 was between $11.6 billion and $19.5 billion, and the direct medical costs ranged from $2 billion to $4 billion. In 1985, Rice and Miller (1996) estimated the financial burden at $22.7 billion of which $11.1 billion was attributable to direct medical costs. Rice’s (1996) estimate updated to 1990 values was $32.5 billion (direct medical cost = $17.3 billion) and that of Wyatt et al. (1995) for 1991 was $65.2 billion, with direct medical costs accounting for about $19 billion. The most recent estimate by Wu et al. (2005) for 2002 costs was $62.7 billion (direct medical costs = $22.7 billion). Another study conducted in 2001-2002 by McDonald et al. (2005) estimated the schizophrenia-associated direct medical costs to $2.13 billion. This wide range of estimates is probably due to differences in study time periods, costs included, measurement of costs, and patient populations.

Conwell and Cohen’s report (2005), based on the 2002 Medical Expenditure Panel Survey (MEPS), a nationally representative annual survey of noninstitutionalized U.S. residents, indicated that 5% of the American population was responsible for 49% of the medical expenditure for all conditions, while half the population was responsible for only 3% of the total expenditures. McDonald et al.’s estimate for the direct cost of schizophrenia showed a similar pattern, where about 0.36% (N = 571,000) of community-dwelling patients with schizophrenia and related psychoses were responsible for $2.13 billion in direct medical costs during 2001-2002. Investigators such as Terkelson and Menikoff (1995) have hypothesized that several factors, such as early onset of disease, presence of comorbid conditions, hospitalizations, need for outpatient and emergency room visits, need for maintenance medications for prolonged periods, and constant requirement of informal support and supervision, are responsible for the high cost of schizophrenia. Identifying characteristics of high-cost patients may be useful for health care providers and managed health care organizations in designing interventions for schizophrenia treatment that target this high-risk population.

Anderson’s Behavioral Model of Health Services Use provides a theoretical framework to understand factors influencing use of health care services. Utilization of health services is associated with costs because higher utilization of health care services leads to higher costs. Andersen’s model includes 3 sets of factors: Predisposing factors include sociodemographic characteristics; enabling factors include those that facilitate or impede the use of health care services; and need factors include indicators of health status. We used Andersen’s model and the literature to identify factors that could potentially be associated with high schizophrenia-related direct medical costs. Several studies have shown that age, gender, insurance status, and presence of comorbid conditions are associated with schizophrenia-related costs. The prevalence of schizophrenia varies by age, gender, race, insurance status, family income as a percentage of poverty line, and marital status. Thus, we also expected the costs to vary by these factors. In addition, we also examined how patient-perceived general health status and mental health status were associated with costs.

Community-dwellers are an important population to consider because in recent years there has been movement towards de-institutionalization due to the Omnibus Budget Reconciliation Act (OBRA) of 1987. Thus, the objective of this study was to determine if significant associations exist between patient demographic and clinical factors and “high” schizophrenia-related direct medical costs among community-dwelling patients using the MEPS database.

**Methods**

The retrospective database analysis used 2005-2008 MEPS data. It was approved by the Institutional Review Board of the University of Texas at Austin. MEPS was first conducted in 1996 and is administered annually for civilian noninstitutionalized Americans. It collects information from individuals and families, their medical providers, and employers. An overlapping panel design is used for this purpose. Each panel collects data over a two-and one-half-year period using 5 rounds of interviews, which yields 2 full years of data. The information collected includes the type, usage frequency, cost, and method of payment for various medical services; detailed insurance information; access to care; satisfaction with care; employment information; and demographic characteristics. MEPS has 3 components: the household component (HC), the medical provider component (MPC), and the insurance component (IC). Information in the HC is collected by self-report, and the MPC is used to validate and supplement information collected in the HC. For the purposes of this study, only the HC information was used. The full-year consolidated data file, medical conditions data file, and the event data files for inpatient hospitalizations, outpatient visits, office-based physician visits, emergency room visits, home health care visits, and prescription medications were merged prior to conducting analyses. Demographic information and expenditure data were utilized for the analyses. Data files from 2005-2008 were combined to obtain the final analytical dataset. Pooling data over several years increases the precision of estimates for the subpopulation of patients with schizophrenia.

Patients with a diagnosis of schizophrenic disorder (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] code 295) and other nonorganic psychoses (ICD-9-CM code 298) were identified from the MEPS data. Patients of all ages, genders, and ethnicities were included in the study. Schizophrenia-related direct medical costs were calculated and summed for the following service utilization categories: inpatient hospitalizations, outpatient
visits, office-based physician visits, emergency room visits, home health care visits, and prescription medications. Outpatient visits included visits to a unit of a hospital or facility connected to a hospital providing health and medical services to individuals who receive services from the hospital but do not require overnight hospitalization. Office-based physician visits included visits to doctors or group practice offices, medical clinics, managed care plans or health maintenance organization centers, neighborhood/family/community health centers, surgical centers, rural health clinics, company clinics, school clinics, walk-in urgent centers, Veterans Administration (VA) facilities, or laboratory/x-ray facilities. Only events associated with an ICD-9-CM code of 295 and 298 were included to ensure that only schizophrenia-related costs were captured in the analysis. The schizophrenia-related direct costs included MEPS-reported amounts paid by the following sources: patient and/or family, Medicare, Medicaid, VA, TRICARE, other federal sources, local and state government sources, worker’s compensation, private insurance, and other sources of insurance. A societal perspective was used for the study. Determinants of high costs were identified based on their relationships with direct medical costs. The cost variable was dichotomized into high-cost (expenditures ≥ $16,000) and low-cost (expenditures < $16,000) groups based on a natural break in the distribution of costs, while ensuring that there were sufficient patients in each group. Demographic and clinical characteristics were compared between the high- and low-cost groups using t-tests (for continuous variables) and Rao-Scott chi-square tests (for categorical variables). Logistic regression was carried out using the dichotomized cost variable as the dependent variable and age, sex, race, marital status, insurance status, family income as a percentage of the federal poverty level, region of residence, patient-perceived general health status, patient-perceived mental health status, number of medical comorbidities, and the number of mental health-related comorbidities as independent variables. Medical comorbidities included hepatic disorder, hyperlipidemia, hypertension, diabetes, obesity, asthma, and human immunodeficiency virus infection/acquired immunodeficiency syndrome. Mental health-related comorbidities included psychiatric diagnoses, anxiety, and substance and alcohol use disorders. Because of the limited sample size, the 95% confidence intervals (CI) of the odds ratios (OR) were very wide. Therefore, a second analytical approach was undertaken using a generalized linear model (GLM) analysis to conduct a regression procedure employing a gamma distribution and a log-link function. Total schizophrenia-related cost (as a continuous variable) was used as the dependent variable, and age, sex, race, marital status, insurance status, region of residence, family income as a percentage of the federal poverty level, patient-perceived general health status, patient-perceived mental health status, number of medical comorbidities, and number of mental health-related comorbidities were used as the independent

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| TABLE 1 | Demographic and Clinical Characteristics of the Schizophrenia Population |
|-----------------|-----------------|-------------------|-------------------|
| **Demographic/ Clinical Characteristics** | **Categories** | **Weighted N** | **Percentage** |
| **Age [mean (SE)]** | | 3,031,572 | 43.1 (1.4) |
| **Sex** | Male | 1,674,993 | 55.2 |
| | Female | 1,356,579 | 44.8 |
| **Race** | Caucasian | 2,152,830 | 71.0 |
| | African American | 719,947 | 23.8 |
| | American Indian/ Alaska Native | 12,467 | 0.4 |
| | Asian | 12,100 | 0.4 |
| | Native Hawaiian/ Pacific Islander | 1,869 | 0.1 |
| | Multiple races reported | 132,359 | 4.4 |
| **Insurance status** | Any private | 617,788 | 20.4 |
| | Public only | 2,192,729 | 72.3 |
| | No insurance | 221,055 | 7.3 |
| **Marital status** | Married | 418,588 | 13.8 |
| | Widowed | 253,304 | 8.4 |
| | Divorced | 589,250 | 19.4 |
| | Separated | 70,639 | 2.3 |
| | Never married | 1,607,544 | 53.0 |
| | Inapplicable-below 16 years | 92,246 | 3.0 |
| **Region of residence** | Northeast | 676,684 | 22.3 |
| | Midwest | 600,036 | 19.8 |
| | South | 1,028,332 | 33.9 |
| | West | 591,077 | 19.5 |
| | Not reported | 135,243 | 4.5 |
| **Family income as a percentage of the federal poverty level** | Poor/negative | 1,031,972 | 34.0 |
| | Poor | 380,824 | 12.6 |
| | Low income | 554,599 | 18.3 |
| | Mid income | 666,674 | 22.0 |
| | High income | 397,503 | 13.1 |
| **Patient-perceived mental health status** | Excellent | 181,964 | 6.0 |
| | Very good | 576,658 | 19.1 |
| | Good | 1,007,110 | 33.3 |
| | Fair | 944,782 | 31.2 |
| | Poor | 314,905 | 10.4 |
| **Patient-perceived mental health status** | Excellent | 84,822 | 2.8 |
| | Very good | 336,678 | 11.1 |
| | Good | 796,205 | 26.3 |
| | Fair | 1,249,139 | 41.3 |
| | Poor | 558,315 | 18.5 |
| **Number of medical comorbidities [mean (SE)]** | 3,031,572 | 0.85 (0.07) |
| **Number of mental health-related comorbidities [mean (SE)]** | 3,031,572 | 1.11 (0.11) |
| **Year** | 2005 | 718,835 | 23.7 |
| | 2006 | 611,240 | 20.2 |
| | 2007 | 893,953 | 29.5 |
| | 2008 | 807,543 | 26.0 |

*Family income as a percentage of the federal poverty level (FPL) was defined as follows: Poor/negative: less than 1.00 times the FPL, Poor: 1.01 to 1.24 times the FPL, Low income: 1.25 to 1.99 times the FPL, Middle income: 2.00 to 3.99 times the FPL, High income: 4.0 or more times the FPL. SE = standard error.
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Results

We identified 348 patients with a diagnosis of schizophrenia in the 2005-2008 MEPS data, which represents 3.03 million noninstitutionalized U.S. residents. Table 1 provides the demographic and clinical characteristics of the schizophrenia population included in this study.

Of the 3.03 million patients with schizophrenia in MEPS, 2.86 million (unweighted frequency = 327) reported having schizophrenia-related direct medical costs. Of those, 2.75 million (unweighted frequency = 317) patients had complete information on all the variables required for the regression procedure, so they were included in subsequent analyses (Figure 1). The average annual cost per patient was $5,402 (standard error [SE] = $580). Figure 2 shows the frequency distribution of the weighted schizophrenia-related direct medical costs for the patients. Based on the distribution, $16,000 was selected as the cutoff point for the high-cost group for the logistic regression procedure. For the regression procedure, some of the categories for race, marital status, family income as a percentage of the federal poverty level, patient-perceived general health status, and patient-perceived mental health status were combined in order to ensure a sufficient sample size in each category. Patients who were unmarried (separated, divorced, widowed, or never married) were grouped together as they would likely have less family support compared with those who were married or under age 16 (and likely to be living with their parents). The sample size for the group of patients under age 16 was too small to make it a separate category.

variables. A modified Park test was used to determine the appropriate model for the analysis.22 This test was conducted by regressing the natural log of the squared residual on the natural log of the predicted value of the dependent variable.23

All analyses were conducted using SAS version 9.2 (SAS Institute Inc., Cary, NC) and Stata version 12 (Stata Corp. LP, College Station, TX). The “survey” procedure of SAS and the “svy” procedure of Stata were used to calculate accurate point estimates and their associated standard errors for the civilian noninstitutionalized population incorporating the MEPS survey weights and accounting for the complex, multistage sampling design of MEPS. The participating individuals in MEPS represent only a fraction of the overall population intended to be reflected by the survey. In order to represent the overall population, responses of the surveyed individuals must be weighted by the proportion of the population they represent. Thus, the person weights provided in the MEPS dataset were used to derive national estimates; these weights take into account poststratification and nonresponse adjustments.

DV = dependent variable; IV = independent variable; M = million.
TABLE 2  Chi-square Analysis of Demographic and Clinical Characteristics by High- and Low-Cost Groups

<table>
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<th>Demographic/Clinical Variables</th>
<th>Categories</th>
<th>Low-Cost Group</th>
<th>High-Cost Group</th>
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<th>P Value</th>
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<td>Weighted N</td>
<td>Percentage</td>
<td>Weighted N</td>
<td>Percentage</td>
</tr>
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<td>82,243</td>
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<td>Marital status</td>
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<td>444,430</td>
<td>17.4</td>
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<td></td>
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<td>168,361</td>
<td>6.6</td>
<td>17,520</td>
<td>8.9</td>
</tr>
<tr>
<td>Region</td>
<td>Northeast</td>
<td>602,839</td>
<td>23.6</td>
<td>53,972</td>
<td>27.3</td>
</tr>
<tr>
<td></td>
<td>Midwest</td>
<td>521,040</td>
<td>20.4</td>
<td>44,189</td>
<td>22.3</td>
</tr>
<tr>
<td></td>
<td>South</td>
<td>961,127</td>
<td>37.7</td>
<td>45,781</td>
<td>23.1</td>
</tr>
<tr>
<td></td>
<td>West</td>
<td>467,628</td>
<td>18.3</td>
<td>53,861</td>
<td>27.2</td>
</tr>
<tr>
<td>Family income as a percentage of federal poverty level</td>
<td>Low incomea</td>
<td>1,621,586</td>
<td>63.5</td>
<td>146,081</td>
<td>73.0</td>
</tr>
<tr>
<td></td>
<td>High incomex</td>
<td>931,049</td>
<td>36.5</td>
<td>51,722</td>
<td>26.2</td>
</tr>
<tr>
<td>Patient-perceived general health status</td>
<td>Excellentf</td>
<td>657,223</td>
<td>25.8</td>
<td>39,304</td>
<td>19.9</td>
</tr>
<tr>
<td></td>
<td>Goodsf</td>
<td>1,664,453</td>
<td>65.2</td>
<td>124,945</td>
<td>63.2</td>
</tr>
<tr>
<td></td>
<td>Poorf</td>
<td>230,999</td>
<td>9.1</td>
<td>33,553</td>
<td>17.0</td>
</tr>
<tr>
<td>Patient-perceived mental health status</td>
<td>Excellentf</td>
<td>338,073</td>
<td>13.2</td>
<td>28,859</td>
<td>14.6</td>
</tr>
<tr>
<td></td>
<td>Goodsf</td>
<td>1,741,993</td>
<td>68.2</td>
<td>144,314</td>
<td>73.1</td>
</tr>
<tr>
<td></td>
<td>Poorf</td>
<td>472,569</td>
<td>18.5</td>
<td>24,430</td>
<td>12.4</td>
</tr>
<tr>
<td>Year</td>
<td>2005</td>
<td>612,120</td>
<td>24.0</td>
<td>62,705</td>
<td>31.7</td>
</tr>
<tr>
<td></td>
<td>2006</td>
<td>498,007</td>
<td>19.5</td>
<td>40,628</td>
<td>20.5</td>
</tr>
<tr>
<td></td>
<td>2007</td>
<td>751,972</td>
<td>29.5</td>
<td>32,548</td>
<td>16.5</td>
</tr>
<tr>
<td></td>
<td>2008</td>
<td>690,537</td>
<td>27.1</td>
<td>61,923</td>
<td>31.3</td>
</tr>
</tbody>
</table>

- American Indian/Alaskan Native, Asian, Native Hawaiian/Pacific Islander, and multiple races reported collapsed into "Other."
- Married and less than aged 16 years collapsed into “Has spouse or is less than 16 years of age.”
- Widowed, divorced, separated, and never married collapsed into “No spouse.”
- Poor/negative, poor, low income collapsed into “Low income.”
- Middle income and high income collapsed into “High income.”
- Excellent and very good collapsed into “Excellent.”
- Good and fair collapsed into “Good.”

There were 197,803 patients (unweighted frequency = 21) in the high-cost group and 2.55 million patients (unweighted frequency = 296) in the low-cost group. The mean cost per patient-year was $3,656 (SE = $283) for the low-cost group and $27,944 (SE = $4,639) for the high-cost group. Descriptive statistics and results of statistical comparisons for the categorical demographic and clinical characteristics by the high- and low-cost groups are reported in Table 2, and those for the continuous demographic and clinical characteristics are provided in Table 3. Table 4 provides the mean costs and the proportions of costs for the different service utilization categories for the low- and high-cost groups. Inpatient hospitalizations (low-cost = 10.1%, high-cost = 28.5%), office-based physician visits (low-cost = 26.8%, high-cost = 24.5%), and prescription medications (low-cost = 52.3%, high-cost = 22.7%) accounted for a large proportion of the expenditures in both groups. Rao-Scott chi-square tests and t-tests demonstrated that there were no statistically significant differences between the 2 groups with respect to demographic or clinical characteristics except for age. Patients in the low-cost group were older than those in the high-cost group (43.7 years vs. 34.6 years; \( P = 0.0021 \)).

A logistic regression procedure was carried out with high- (≥ $16,000) and low- (< $16,000) cost categories (based on direct costs) as the dependent variable and age, gender, race, marital status, insurance coverage, family income as a percentage of the federal poverty level, region of residence, patient-perceived general health status, patient-perceived mental health status, number of medical comorbidities, and the number of mental health-related comorbidities as the independent variables. Table 5 provides the regression coefficients,
Identifying Patient Characteristics Associated with High Schizophrenia-Related Direct Medical Costs in Community-Dwelling Patients

### Table 3: T-test Analysis of Demographic and Clinical Characteristics by High- and Low-Cost Groups

<table>
<thead>
<tr>
<th>Demographic/Clinical Variables</th>
<th>Low-Cost Group</th>
<th>High-Cost Group</th>
<th>T-statistic</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>43.70 (1.40)</td>
<td>43.60 (2.90)</td>
<td>-3.09</td>
<td>0.002</td>
</tr>
<tr>
<td>Number of clinical comorbidities</td>
<td>0.88 (0.08)</td>
<td>0.71 (0.22)</td>
<td>-0.78</td>
<td>0.434</td>
</tr>
<tr>
<td>Number of mental health-related comorbidities</td>
<td>1.18 (0.11)</td>
<td>0.98 (0.39)</td>
<td>-0.53</td>
<td>0.598</td>
</tr>
</tbody>
</table>

*P < 0.05. SE = standard error.

### Table 4: Mean Costs Per Patient by Health Care Utilization Category for the Low- and High-Cost Groups

<table>
<thead>
<tr>
<th>Cost Category</th>
<th>Low-Cost Mean (SE) [%]</th>
<th>High-Cost Mean (SE) [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inpatient hospitalizations</td>
<td>$367.76 ($104.62)</td>
<td>$7,962.18 ($3,133.80)</td>
</tr>
<tr>
<td>Outpatient visits</td>
<td>$93.98 ($31.24)</td>
<td>$653.39 ($574.80)</td>
</tr>
<tr>
<td>Office-based physician visits*</td>
<td>$979.66 ($154.65)</td>
<td>$6,836.61 ($1,799.28)</td>
</tr>
<tr>
<td>Emergency room visits</td>
<td>$17.93 ($7.23)</td>
<td>$237.14 ($166.07)</td>
</tr>
<tr>
<td>Home health care visits</td>
<td>$280.40 ($111.49)</td>
<td>$5,933.25 ($3,613.74)</td>
</tr>
<tr>
<td>Prescription medications</td>
<td>$1,915.85 ($175.84)</td>
<td>$6,338.95 ($1,449.93)</td>
</tr>
<tr>
<td>Total</td>
<td>$3,056 ($283)</td>
<td>$27,944 ($4,639)</td>
</tr>
</tbody>
</table>

*Includes physical therapy, occupational therapy, speech therapy, chemotherapy, radiation therapy, kidney dialysis, intravenous therapy, drug or alcohol treatment, allergy shots, psychotherapy/counseling, and shots other than for allergy treatment. SE = standard error.

Wald's chi-square values, ORs, and 95% CIs of the ORs for all the variables included in the model.

The overall model was statistically significant (Wald's chi-square = 42.26, degree of freedom [df] = 20; P = 0.001). After controlling for the other variables, age, marital status, and perceived general health status were found to be statistically significantly associated with high-cost group membership. With a 1-year increase in age, patients were 6.7% less likely to be in the high-cost group (OR = 0.933, 95% CI = 0.902-0.966). Patients who had a spouse or were under aged 16 years were 85.0% less likely than those without a spouse to be in the high-cost group (OR = 0.150, 95% CI = 0.041-0.555). Patients who reported having a poor self-perceived general health status were 15.6 times more likely to be in the high-cost group compared with those who reported having an excellent self-perceived general health status (OR = 15.548, 95% CI = 1.278-189.127). Gender, race, insurance status, region of residence, family income as a percentage of the federal poverty level, patient-perceived mental health status, and presence of medical or mental health-related comorbidities were not significantly related to high-cost group membership.

Because of the limited sample size, some of the CIs of the ORs were very wide, raising questions about the accuracy of the estimates. In addition, the cost data were positively skewed.

### Table 5: Results of Logistic Regression Procedure—Predicting High-Cost Group Membership for Dichotomized Schizophrenia-Related Direct Medical Costs by Demographic and Clinical Variables

<table>
<thead>
<tr>
<th>Demographic/Clinical Variables (Reference Group)</th>
<th>Estimate</th>
<th>Wald's Chi-square</th>
<th>P Value</th>
<th>Odds Ratio</th>
<th>95% CI of Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>-0.0689</td>
<td>15.5185</td>
<td>&lt;0.001</td>
<td>0.933</td>
<td>0.902-0.966</td>
</tr>
<tr>
<td>Sex (males)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Females</td>
<td>-0.0396</td>
<td>0.0168</td>
<td>0.892</td>
<td>0.924</td>
<td>0.279-3.062</td>
</tr>
<tr>
<td>Race (African American)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>-0.6899</td>
<td>2.3280</td>
<td>0.127</td>
<td>0.430</td>
<td>0.109-1.689</td>
</tr>
<tr>
<td>Other</td>
<td>0.5351</td>
<td>0.9164</td>
<td>0.338</td>
<td>1.463</td>
<td>0.230-8.532</td>
</tr>
<tr>
<td>Marital status (no spouse)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Has spouse or under aged 16 years*</td>
<td>-0.9484</td>
<td>8.0711</td>
<td>0.005</td>
<td>0.315</td>
<td>0.041-0.555</td>
</tr>
<tr>
<td>Insurance coverage (private insurance)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Public insurance</td>
<td>0.1898</td>
<td>0.2821</td>
<td>0.595</td>
<td>0.978</td>
<td>0.214-4.463</td>
</tr>
<tr>
<td>No insurance</td>
<td>-0.4018</td>
<td>0.4600</td>
<td>0.498</td>
<td>0.541</td>
<td>0.059-4.925</td>
</tr>
<tr>
<td>Region (Northeast)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Midwest</td>
<td>0.1481</td>
<td>0.1043</td>
<td>0.747</td>
<td>1.109</td>
<td>0.277-4.449</td>
</tr>
<tr>
<td>South</td>
<td>0.6861</td>
<td>2.3809</td>
<td>0.123</td>
<td>0.482</td>
<td>0.121-1.923</td>
</tr>
<tr>
<td>West</td>
<td>0.4935</td>
<td>1.5735</td>
<td>0.210</td>
<td>1.567</td>
<td>0.458-5.363</td>
</tr>
<tr>
<td>Family income as a percentage of federal poverty level (high income)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low income</td>
<td>-0.2208</td>
<td>0.3193</td>
<td>0.572</td>
<td>0.643</td>
<td>0.139-2.975</td>
</tr>
<tr>
<td>Patient-perceived general health status (excellent)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Good</td>
<td>-0.2743</td>
<td>0.4414</td>
<td>0.506</td>
<td>2.613</td>
<td>0.456-14.989</td>
</tr>
<tr>
<td>Poor</td>
<td>1.5091</td>
<td>5.0910</td>
<td>0.024</td>
<td>15.548</td>
<td>1.278-189.127</td>
</tr>
<tr>
<td>Patient-perceived mental health status (excellent)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Good</td>
<td>0.1233</td>
<td>0.0640</td>
<td>0.800</td>
<td>0.543</td>
<td>0.066-4.439</td>
</tr>
<tr>
<td>Poor</td>
<td>-0.8577</td>
<td>0.5460</td>
<td>0.116</td>
<td>0.203</td>
<td>0.021-1.953</td>
</tr>
<tr>
<td>Number of medical comorbidities</td>
<td>0.1333</td>
<td>0.2271</td>
<td>0.634</td>
<td>1.143</td>
<td>0.660-1.977</td>
</tr>
<tr>
<td>Number of mental health-related comorbidities</td>
<td>-0.3710</td>
<td>1.3095</td>
<td>0.253</td>
<td>0.690</td>
<td>0.366-1.303</td>
</tr>
<tr>
<td>Year (2005)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2006</td>
<td>0.3009</td>
<td>0.3575</td>
<td>0.550</td>
<td>1.098</td>
<td>0.230-5.243</td>
</tr>
<tr>
<td>2007</td>
<td>-0.6767</td>
<td>1.4923</td>
<td>0.222</td>
<td>0.413</td>
<td>0.075-2.269</td>
</tr>
<tr>
<td>2008</td>
<td>0.1686</td>
<td>0.1467</td>
<td>0.702</td>
<td>0.962</td>
<td>0.229-4.048</td>
</tr>
</tbody>
</table>

*P < 0.05. CI = confidence interval.
TABLE 6: Results of GLM Regression Procedure for Schizophrenia-Related Direct Medical Costs by Demographic and Clinical Variables

<table>
<thead>
<tr>
<th>Demographic/ Clinical Variables (Reference Group)</th>
<th>Estimate</th>
<th>Linearized Standard Errors</th>
<th>T-statistic</th>
<th>P Value</th>
<th>95% CI of Point Estimate</th>
<th>Lower</th>
<th>Higher</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.9778</td>
<td>0.0055</td>
<td>-3.93</td>
<td>&lt;0.001</td>
<td>0.9669</td>
<td>0.9889</td>
<td></td>
</tr>
<tr>
<td>Sex (Males)</td>
<td>0.9703</td>
<td>0.1772</td>
<td>-0.17</td>
<td>0.869</td>
<td>0.6767</td>
<td>1.3913</td>
<td></td>
</tr>
<tr>
<td>Race (African American)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>0.5058</td>
<td>0.1258</td>
<td>-2.74</td>
<td>0.007</td>
<td>0.3097</td>
<td>0.8263</td>
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</tr>
<tr>
<td>Other</td>
<td>0.6603</td>
<td>0.3061</td>
<td>-0.90</td>
<td>0.372</td>
<td>0.2645</td>
<td>1.4683</td>
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</tr>
<tr>
<td>Marital status (no spouse)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Has spouse or is under aged 16 years</td>
<td>0.6861</td>
<td>0.1587</td>
<td>-1.63</td>
<td>0.105</td>
<td>0.4346</td>
<td>1.0830</td>
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</tr>
<tr>
<td>Insurance coverage (private)</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Public insurance</td>
<td>1.2107</td>
<td>0.2953</td>
<td>0.73</td>
<td>0.434</td>
<td>0.7482</td>
<td>1.9592</td>
<td></td>
</tr>
<tr>
<td>No insurance</td>
<td>0.4081</td>
<td>0.1637</td>
<td>-2.23</td>
<td>0.027</td>
<td>0.1849</td>
<td>0.9008</td>
<td></td>
</tr>
<tr>
<td>Region (Northeast)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Midwest</td>
<td>0.8299</td>
<td>0.2244</td>
<td>-0.69</td>
<td>0.492</td>
<td>0.4867</td>
<td>1.4152</td>
<td></td>
</tr>
<tr>
<td>South</td>
<td>0.5432</td>
<td>0.1272</td>
<td>-2.61</td>
<td>0.010</td>
<td>0.3422</td>
<td>0.8624</td>
<td></td>
</tr>
<tr>
<td>West</td>
<td>1.0612</td>
<td>0.2962</td>
<td>0.21</td>
<td>0.832</td>
<td>0.6183</td>
<td>1.5452</td>
<td></td>
</tr>
<tr>
<td>Family income as a percentage of federal poverty level (high income)</td>
<td>0.7729</td>
<td>0.1544</td>
<td>-1.29</td>
<td>0.199</td>
<td>0.5211</td>
<td>1.1464</td>
<td></td>
</tr>
<tr>
<td>Patient-perceived general health status (excellent)</td>
<td>0.9562</td>
<td>0.2318</td>
<td>-0.18</td>
<td>0.851</td>
<td>0.5926</td>
<td>1.5430</td>
<td></td>
</tr>
<tr>
<td>Poor</td>
<td>1.1529</td>
<td>0.4756</td>
<td>-0.34</td>
<td>0.731</td>
<td>0.5107</td>
<td>2.0250</td>
<td></td>
</tr>
<tr>
<td>Patient-perceived mental health status (excellent)</td>
<td>1.3666</td>
<td>0.4149</td>
<td>1.03</td>
<td>0.305</td>
<td>0.7506</td>
<td>2.4880</td>
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</tr>
<tr>
<td>Poor</td>
<td>1.4862</td>
<td>0.5662</td>
<td>1.04</td>
<td>0.300</td>
<td>0.7007</td>
<td>3.1522</td>
<td></td>
</tr>
<tr>
<td>Number of medical comorbidities</td>
<td>1.11584</td>
<td>0.0584</td>
<td>1.72</td>
<td>0.086</td>
<td>0.9789</td>
<td>1.3707</td>
<td></td>
</tr>
<tr>
<td>Number of mental-health related comorbidities</td>
<td>0.9140</td>
<td>0.0988</td>
<td>-1.41</td>
<td>0.162</td>
<td>0.8057</td>
<td>1.0370</td>
<td></td>
</tr>
<tr>
<td>Year (2005)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2006</td>
<td>1.1928</td>
<td>0.3333</td>
<td>0.63</td>
<td>0.529</td>
<td>0.6873</td>
<td>2.0703</td>
<td></td>
</tr>
<tr>
<td>2007</td>
<td>0.9391</td>
<td>0.2491</td>
<td>-0.24</td>
<td>0.813</td>
<td>0.5564</td>
<td>1.5850</td>
<td></td>
</tr>
<tr>
<td>2008</td>
<td>0.9171</td>
<td>0.2410</td>
<td>-0.33</td>
<td>0.742</td>
<td>0.5459</td>
<td>1.5405</td>
<td></td>
</tr>
</tbody>
</table>

*P < 0.05.

CI = confidence interval; GLM = generalized linear model.

Therefore, a separate regression was carried out using a GLM (employing a gamma distribution with a log-link function) to evaluate the relationships between the independent variables and the schizophrenia-related direct costs as a continuous variable (Table 6). Model selection was based on the modified Park test, which gave a coefficient of 1.99, indicating a gamma distribution. Age, race, insurance coverage, and region of residence were found to be statistically significantly associated with costs, while controlling for all other factors. With a 1-year increase in age, on average, the schizophrenia-related direct costs decreased by a factor of 0.98 (t-statistic = -3.93; P < 0.001). The ratio of the schizophrenia-related direct medical costs for Caucasian patients and African American patients was 0.51 (t-statistic = -2.74; P = 0.007); thus, Caucasian patients had lower costs than African American patients. Patients with no insurance had lower schizophrenia-related direct costs than those with private insurance, and the ratio of the mean costs for the 2 was 0.41 (t-statistic = -2.23; P = 0.027). Patients who lived in the southern United States spent less on schizophrenia-related direct costs compared with those living in the northeastern United States, and the ratio of the mean costs was 0.54 (t-statistic = -2.61; P = 0.010). Because of the difficulty in interpreting arithmetic mean ratios, we calculated the average marginal effects for each significant variable. However, it should be noted that for continuous variables, the interpretation of the average marginal effects holds only for an infinitesimal change in the independent variable. For larger changes, the values depend on the nature of the relationship between the independent and dependent variables. With a 1-year increase in age, the schizophrenia-related direct medical costs decreased by $125. Caucasian patients spent $3,803 less than African American patients on schizophrenia-related direct medical costs. Uninsured patients spent $5,003 less than those with private insurance on schizophrenia-related costs. Schizophrenia-related expenditures for patients residing in the southern United States were $3,406 less than those residing in the northeastern United States.

Sensitivity Analysis

Because the cutoff point for the high-cost group was relatively high, a sensitivity analysis was conducted using a lower cutoff point for the high-cost group ($5,402), which was also the mean cost for all patients. There were 812,703 (unweighted frequency = 90) patients in the high-cost group, and 1.94 million patients (unweighted frequency = 227) in the low-cost group. The bivariate analyses showed no difference with respect to any of the demographic and clinical characteristics except region of residence. A greater proportion of patients in the low-cost group, compared with the high-cost group, resided in the southern United States (42.7% vs. 22.0%), whereas a lower proportion of patients in the low-cost group, compared with the high-cost group, resided in the northeastern United States (19.9% vs. 33.4%); (P = 0.0378). The logistic regression procedure showed that after controlling for all other factors, patients in the South were 70.0% less likely to be in the high-cost group compared with those in the Northeast (OR = 0.300, 95% CI = 0.120-0.752; P = 0.0024). It was also seen that as the number of medical comorbidities increased by a single unit, patients were 1.4 times more likely to be in the high-cost group (OR = 1.384, 95% CI = 1.005-1.906; P = 0.0464). The tables for the bivariate and logistic regression procedures using the high-cost threshold of $5,402 are provided in the Appendices (available online).

When $16,000 was used as the cutoff for the high-cost...
group, the unadjusted analyses demonstrated that the high-
and low-cost groups differed significantly on age; when the
 cutoff was reduced to $5,402, the unadjusted analyses dem-
onstrated statistically significant difference between the 2
groups with respect to region of residence. The results obtained
from the logistic regression procedures also differed; when $16,000
was used as the cutoff for the high-cost group, age, marital sta-
tus, and patient-perceived general health status were found to
be significantly associated with high-cost group membership.
With $5,402 as the cutoff, region of residence and number of
mental health comorbidities were found to be significant pre-
dictors of high-cost group membership.

Discussion
Based on our review of the literature, this is the first study to
use a multivariate logistic regression approach to identify fac-
tors associated with high schizophrenia-related costs in the
United States. The logistic regression procedure demonstrated
a significant negative relationship between age and high-cost
group membership. Other studies have shown negative rela-
tionships between age and schizophrenia-related costs. Dixon
et al. (2001) found that younger patients were associated with
greater utilization and costs associated with ambulatory care
services. Bartels et al. (2003) found that younger patients
were associated with higher expenditures for medications and
outpatient services, while older patients were associated with
higher nursing home costs. Although our study included
home health care costs and inpatient costs, it did not include
nursing home costs, which could explain the negative relation-
ship found between age and costs. A similar negative relation-
ship between age and schizophrenia-related costs was also
observed by Rascati et al. (2003).

Patients with a spouse or those under age 16 had sig-
nificantly lower schizophrenia-related expenditures compared
with those without a spouse. One possible explanation for this
finding is the presence of family support, which may have led to
more proactive medication-taking behaviors and less use of
expensive services, resulting in decreased overall schizophre-
nia-related direct medical costs. Contrary to our expectations,
marrried patients and those under age 16 had lower prescription
drug costs ($1,301 [SE = $306] vs. $2,419 [SE = $262]) and
higher inpatient hospitalization costs ($1,587 [SE = $803] vs. $780
[SE = $278]) compared with the unmarried patients. However,
the married patients and patients under age 16 had lower costs
for other expensive services, such as home health care visits
($121 [SE = $101] vs. $799 [SE = $348]) and office-based physi-
cian visits ($1,237 [SE = $564] vs. $1,433 [SE = $249]). Previous
research has shown that patients with poor perceived general
health status are more likely to utilize health care services,
which translates into higher health care costs.

Because the limited sample size within each cost category
may have led to unstable OR estimates, a GLM regression
using a gamma distribution and log-link function was carried
out. The GLM regression procedure showed that age, race,
insurance status, and region of residence were significantly
associated with schizophrenia-related direct costs. A nega-
tive association between age and schizophrenia-related direct
costs was observed in the study by Bartels et al. A similar
association was also observed in the logistic and linear regres-
sion analyses of the current study. Dixon et al. observed
that Caucasians had higher expenditures as compared with
African Americans; however, the opposite was observed in
this study. One potential explanation is higher utilization of
more expensive services (e.g., inpatient hospitalizations, home
health care) among African Americans. The lower costs among
the uninsured is probably due to lower utilization of routine
services because of lack of insurance, since expenditures such
as prescription medications and physician office visits make up
a large proportion of the schizophrenia-related direct costs
for community-dwellers. Although we had more schizophrenia
patients in the southern states as compared with the north-
eastern states (contrary to that reported by Torrey and Bowler
[1990]), the higher costs in the Northeast are likely due to more
expensive health care services in this region.

Neither the bivariate analysis nor the regression analysis
showed a significant relationship between the number of
comorbidities and costs. However, the nature of the relation-
ship was reversed for the 2 analyses. The unadjusted analysis
(t-test) showed that patients in the high-cost group had fewer
comorbidities than those in the low-cost group, whereas the
regression analyses showed that, after controlling for other
factors, the number of medical comorbidities was positively
associated with costs. The small sample size likely played a
role in the lack of statistical significance. The number of mental
health-related comorbidities was lower for the high-cost group
in both the unadjusted and adjusted analyses. This trend was
also observed by Rascati et al. in which patients with a history
of mental illnesses were associated with lower schizophrenia-
related costs.

The results of the sensitivity analyses demonstrate that the
statistical significance associated with the predictors was sen-
sitive to the definition used for the high-cost group. Logistic
regression using $16,000 as the cutoff point showed that age,
marital status, and patient-perceived general health status were
significant predictors of high-cost group membership, when
$5,402 was used as the cutoff, region of residence and number of
medical comorbidities were significant predictors. Thus, the
logistic regression results vary depending on the choice of
high-cost cutoff points, a situation that is avoided in the GLM.

Identifying the characteristics of the high-risk popula-
tion may help health care providers at the grass roots level
to be mindful of patients most likely to have high expendi-
tures. Demographic characteristics are easily identifiable. Plan
coordinators can assign case managers to these patients early
on during the course of their disease, and health care providers
could encourage these patients to have regular physician visits
Identifying Patient Characteristics Associated with High Schizophrenia-Related Direct Medical Costs in Community-Dwelling Patients

and to carefully follow their medication treatment regimens. Improving continuity of antipsychotic medications and having regular physician visits could help control costs by preventing expensive services such as inpatient hospitalizations. At the health plan level, consideration of the effects of formulary coverage decisions, formulary tier placement, and prior authorization requirements on high-cost patients may be helpful in achieving desired outcomes. High-cost patients could also be potential candidates for medication therapy management services by pharmacists, which could encourage them to improve medication management and adherence and could potentially lead to lower health care costs.

Limitations
There are some limitations to this study that affect interpretation of the results. Due to the low prevalence of schizophrenia, 4 years of MEPS data were pooled to obtain a sufficiently large sample size to yield reliable estimates. The samples from consecutive years may not be completely independent because the samples are drawn from the same geographic region, and several patients may be in the sample for 2 consecutive years. Therefore, some of the observations for the regression procedures, which were carried out on a sample of all the patients with schizophrenia between 2005 and 2008, are not independent. However, if the costs for the same patient from consecutive years were added, then costs from 2 years would be counted for patients with schizophrenia from 2006 and 2007, while costs from only 1 year would be counted for patients from 2005 and 2008 (the first and last year included in the analyses), which would lead to inaccurate per-person and per-year estimates. In order to avoid this inconsistency, we chose to treat the patients in each year as independent observations. According to MEPS documentation, it is valid to keep all observations and treat them as independent, since each year’s data are designed to be nationally representative. In order to ensure that accurate standard errors are obtained, the survey procedure of SAS and the “svy” procedure of Stata were used for the analysis, as it accounts for the complex sampling design of MEPS.

Despite combining 4 years of MEPS data to ensure a sufficiently large sample size, some of the categories for the independent variables in the logistic regression procedure had a smaller than desired sample size. This may affect the reliability of those estimates. However, studies have been conducted in the past using MEPS for the same disease state.

Since the household component of MEPS consists of noninstitutionalized community-dwelling residents, schizophrenia patients living in supported living facilities, nursing homes, institutions, and prisons were not included. Homeless people and undocumented immigrants were also not included, and they are likely to incur high costs. Thus, the studied population is not representative of all schizophrenia patients in the United States. The subjects for the current study consist of community-dwelling schizophrenia patients who are likely to be higher functioning and less severely ill.

Patients were identified using ICD-9-CM codes only. Because of the stigma associated with the disease, physicians are known to give interim nonschizophrenia diagnoses, when uncertain, until schizophrenia can be confirmed. In addition, the conditions in MEPS are self-reported by the patients. This could lead to under-representation of schizophrenia patients.

Only schizophrenia-related direct medical costs were included in this study. Costs associated with comorbidities potentially related to schizophrenia were excluded because of the difficulties in establishing a causal relationship between schizophrenia and those comorbidities in a cross-sectional dataset such as MEPS.

Conclusion
This is the first study that attempted to identify the characteristics of schizophrenia patients associated with high schizophrenia-related direct costs in the noninstitutionalized U.S. population. A number of demographic and clinical factors were included in the analysis. The characteristics associated with high-cost group membership were identified using logistic regression. In addition, a GLM regression was carried out to determine the association between the demographic and clinical factors and direct costs related to schizophrenia. A modified Park test was used to determine the appropriate distribution for the model prior to conducting the GLM regression.

In recent years, policymakers and researchers have been trying to find ways to improve the delivery of health care while controlling increases in health care costs, especially for the subset of patients who are responsible for a disproportionately large share of overall health care expenditures. This study helps identify community-dwelling schizophrenia patients who are responsible for a disproportionately high level of schizophrenia-related health care expenditures. Identifying the high-cost population may help policymakers allocate resources more efficiently and health care providers manage patients more effectively through assignment of high-risk patients to case managers and appropriate monitoring and treatment.

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Identifying Patient Characteristics Associated with High Schizophrenia-Related Direct Medical Costs in Community-Dwelling Patients

DISCLOSURES
No funding was received for this study. The authors report no conflict of interest regarding this study.
Study concept and design were contributed equally by Desai, Lawson, Barber, and Rascati. Desai had primary responsibility for data collection with assistance from Lawson, Barber, and Rascati. All authors shared equally in data interpretation. The manuscript was written and revised primarily by Desai and Lawson with assistance from Barber and Rascati.

REFERENCES
### Identifying Patient Characteristics Associated with High Schizophrenia-Related Direct Medical Costs in Community-Dwelling Patients

<table>
<thead>
<tr>
<th>Demographic/Clinical Variables</th>
<th>Categories</th>
<th>Low-Cost Group</th>
<th>High-Cost Group</th>
<th>Rao-Scott Chi-square Statistic</th>
<th>P Value</th>
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<td>Percentage</td>
<td>Weighted N</td>
<td>Percentage</td>
<td></td>
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<td></td>
<td>Othera</td>
<td>82,208</td>
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<td>373,645</td>
<td>19.3</td>
<td>81,643</td>
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<tr>
<td></td>
<td>No spousec</td>
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<td>80.7</td>
<td>731,060</td>
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<td>Private insurance</td>
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<td>19.9</td>
<td>271,606</td>
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<td></td>
<td>Midwest</td>
<td>370,215</td>
<td>19.1</td>
<td>195,014</td>
<td>24.0</td>
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<td>South</td>
<td>828,071</td>
<td>42.7</td>
<td>178,837</td>
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<td></td>
<td>West</td>
<td>354,243</td>
<td>18.3</td>
<td>167,246</td>
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<td>Family income as a percentage of federal poverty level</td>
<td>Low income⁴</td>
<td>1,251,748</td>
<td>64.6</td>
<td>515,919</td>
<td>63.5</td>
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<td>High income⁵</td>
<td>685,986</td>
<td>35.4</td>
<td>296,785</td>
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<td>Patient-perceived general health status</td>
<td>Excellentf</td>
<td>472,934</td>
<td>24.4</td>
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<td></td>
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<td>1,271,973</td>
<td>65.6</td>
<td>517,424</td>
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<td>9.0</td>
<td>101,162</td>
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<td>11.4</td>
<td>162,510</td>
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<td>24.2</td>
<td>206,015</td>
<td>25.3</td>
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<td></td>
<td>2006</td>
<td>374,615</td>
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<td>29.3</td>
<td>216,281</td>
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<td>2008</td>
<td>526,073</td>
<td>27.1</td>
<td>226,387</td>
<td>27.9</td>
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</table>

⁴American Indian/Alaskan Native, Asian, Native Hawaiian/Pacific Islander, and multiple races reported collapsed into “Other.”
⁵Married and less than aged 16 years collapsed into “Has spouse or is less than 16 years of age.”
⁶Widowed, divorced, separated, and never married collapsed into “No spouse.”
⁷Poor/negative, poor, and low income collapsed into “Low income.”
⁸Mid income and high income collapsed into “High income.”
⁹Excellent and very good collapsed into “Excellent.”
¹⁰Good and fair collapsed into “Good.”

### APPENDIX B

#### T-test Analysis of Demographic and Clinical Characteristics by High- and Low-Cost Groups Using $5,402 as Cutoff for High-Cost Group

<table>
<thead>
<tr>
<th>Demographic/Clinical Variables</th>
<th>Low-Cost Group</th>
<th>High-Cost Group</th>
<th>T-statistic</th>
<th>P Value</th>
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<td>1.6</td>
<td>40.7</td>
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<td>0.09</td>
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<td>Number of mental health-related comorbidities</td>
<td>1.22</td>
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<td>1.04</td>
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</table>

SE = standard error.
## Identifying Patient Characteristics Associated with High Schizophrenia-Related Direct Medical Costs in Community-Dwelling Patients

### APPENDIX C Results of Logistic Regression Procedure: Predicting High-Cost Group Membership for Dichotomized Schizophrenia-Related Direct Medical Costs by Demographic and Clinical Variables Using $5,402 as Cutoff for High-Cost Group

<table>
<thead>
<tr>
<th>Demographic/Clinical Variables (Reference Group)</th>
<th>Estimate</th>
<th>Wald's Chi-square</th>
<th>P Value</th>
<th>Odds Ratio</th>
<th>95% CI of Odds Ratio</th>
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<td>1.384</td>
<td>1.005</td>
</tr>
<tr>
<td>Number of mental health-related comorbidities</td>
<td>-0.1372</td>
<td>0.8232</td>
<td>0.3642</td>
<td>0.872</td>
<td>0.648</td>
</tr>
<tr>
<td>Year (2005)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.173</td>
</tr>
<tr>
<td>2006</td>
<td>0.1255</td>
<td>0.2283</td>
<td>0.6328</td>
<td>1.054</td>
<td>0.394</td>
</tr>
<tr>
<td>2007</td>
<td>-0.1150</td>
<td>0.2178</td>
<td>0.6407</td>
<td>0.829</td>
<td>0.320</td>
</tr>
<tr>
<td>2008</td>
<td>-0.0833</td>
<td>0.2892</td>
<td>0.7734</td>
<td>0.855</td>
<td>0.325</td>
</tr>
</tbody>
</table>

^aP < 0.05. CI = confidence interval.
Influence of Coadministration of Antithrombotic Medicines, Warfarin, and NSAIDs on Heparin Safety: Data from a Prospective Observational Study

Gabriele Pranckeviciene, MPharm; Edmundas Kadusevicius, MPharm, MD, PhD; and Asta Putniene, MPharm

ABSTRACT

BACKGROUND: Utilization of heparins has been increasing in the last decade, thus, in-depth analysis is needed to assess heparins safety monitoring patterns, incidence rates of adverse drug reactions (ADR), and frequency of coadministration with other medicines.

OBJECTIVE: To investigate the safety monitoring of heparin in hospitals and the influence of coadministration of nonsteroidal anti-inflammatory drugs (NSAIDs), antithrombotic medicines, and warfarin on heparin safety.

METHODS: We reviewed hospital records of 339 patients who had orders for heparin or low molecular weight heparin from May 2009 to May 2010. IBM SPSS Statistics version 18.0 was used to perform statistical analysis.

RESULTS: Dalteparin (n = 238, 70.21%) was the most frequently prescribed heparin. The most frequent indications given were for prophylaxis of venous thrombosis (n = 135, 39.82%) and treatment of unstable coronary artery disease and myocardial infarction (n = 166, 48.97%). ADRs were reported for 75 patients (22.12%), including coagulation abnormalities in 25 patients (7.37%), renal dysfunctions in 24 patients (7.08%), and thrombocytopenia in 10 patients (2.95%). 256 patients (75.52%) had relative contraindications. ADRs were associated with the previously reported relative contraindications (Spearman’s rank correlation coefficient $r_s = 0.261$, Pearson’s chi-squared test $\chi^2 = 45.5$, $P < 0.0005$) and with prolonged treatment with warfarin ($r_s = 0.279$ and $\chi^2 = 74.7$, $P < 0.0005$). ADRs were not related to heparin use but indicated increased risk for negative treatment outcomes. Coadministration of heparin with warfarin, acetylsalicylic acid, clopidogrel, ketorolac, and NSAIDs was associated with the increased risk of adverse drug reactions. The relationship was low but statistically significant. The strongest relationship was with coadministration of aspirin ($r_s = 0.283$, $\chi^2 = 21.42$, $P < 0.0005$), while the coadministration of NSAIDs showed only a very weak relationship to the development of ADRs ($r_s = 0.133$, $\chi^2 = 21.01$, $P < 0.0005$). For the development of thrombocytopenia, the strongest risk was calculated for coadministration of warfarin ($r_s = 0.248$, $\chi^2 = 28.14$, $P < 0.0005$), while coadministration of medicines from the list did not have a relationship with the risk of thrombocytosis.

CONCLUSIONS: Safety monitoring of heparin orders is essential, especially for patients with relative contraindications during long-term treatment and in case of coadministration of oral anticoagulants, platelet inhibitors, and NSAIDs.

What is already known about this subject

- Monitoring of drug treatment can have several benefits: better selection of the appropriate drug therapy, improved adherence to clinical guidelines, and, as a result, improved treatment outcomes. Moreover, monitoring can also help in the identification of potential adverse drug reactions.
- Despite the fact that the value of monitoring is confirmed, a number of published studies report very low compliance in the monitoring of heparin usage in different countries.

What this study adds

- Descriptive analyses were performed and published that characterize heparin use, patient safety, and compliance with national prescribing guidelines at particular hospitals in several countries, although there were no such data available for Lithuania.
- The study results highlighted the fact that there were some gaps in the orders and documentation of information regarding the use of low-molecular-weight heparin (LMWH). Thus, we concluded that implementation of national guidelines on the use of LMWH should be prioritized.
- The results of our study confirmed the very low adherence of LMWH effectiveness and safety monitoring in local hospitals in comparison with international standards. The periodic evaluation of real-life practices may improve adherence to guidelines and potentially improve clinical outcomes.

Monitoring of drug treatment can ensure better selection of the appropriate drug therapy, improved adherence to clinical guidelines, and, as a result, improved treatment outcomes. Moreover, monitoring can also help in the identification of potential adverse drug reactions (ADRs). Monitoring might be defined as the prospective supervision, observation, and testing of an ongoing process. Monitoring provides reassurance that the goal has been or will be achieved or suggests changes that will allow it to be achieved. Therapeutic drug monitoring has typically concentrated on the efficacy and safety of drugs and their concentrations to achieve benefit, avoid harm, or both. Patients and their clinicians can also monitor the progress of a disease and adjust treatment...
accompanying. However, very little consideration has been given to developing effective schemes for monitoring the occurrence of ADRs, such as biochemical or hematological disturbances. Yet monitoring treatment to anticipate or detect adverse reactions to drugs before they become inevitable or irreversible is clearly important.

We selected unfractionated heparin (UFH) and low-molecular-weight-heparins (LMWH) for our evaluation. The utilization of heparins has been increasing over the past decade. The comprehensive list of indications for this pharmaceutical category illustrates how frequently these drugs are used in daily medical practice. Worldwide heparin utilization trends have shown 10% to 15% yearly growth in the past decade. These medicines were primarily used in the inpatient setting, and heparins consumed up to 10% of the total medication costs in hospitals. For example, in Lithuania, the utilization of heparins increased from 322,000 defined daily doses (DDDs) in 2003 to 2,074,000 DDDs in 2010—greater than a 6-fold increase—while total heparin expenditures increased almost 9-fold during this period, from 1,088,000 Lithuanian litas (LTLs) in 2003 up to 9,395,000 LTLs in 2010. Expenditures demonstrated a tendency to increase markedly faster than could be explained by the increased utilization rate of heparin in the country. Therefore, it was important to identify reasons behind that disproportional growth and to anticipate relevant actions that could be taken to manage costs. Thus, it was very important to investigate if the heparins and LMWHs were rationally used in daily medical practice.

Several descriptive analyses were performed and published by other authors that characterize heparins’ use, patient safety, and compliance with national prescribing guidelines at particular hospitals in many countries to improve safe use of heparins in hospital practice.

Methods

Study Objectives

The primary objective of this prospective observational study was to investigate safety monitoring patterns of heparin therapy by assessing the incidence rate of heparin ADRs, the influence of co-orders with nonsteroidal anti-inflammatory drugs (NSAIDs), antithrombotic medicines, and warfarin on ADRs associated with the use of LMWH, the reporting of ADRs to medical records and national pharmacovigilance databases, and adherence to safety monitoring guidelines.

Study Location

This study was conducted at a secondary-level clinical hospital in the second largest city in Lithuania. We anticipated that such a hospital would accurately represent the average secondary-level health care services provider in the country.

Study Population

All patients over 18 years of age who were admitted to the city hospital and received at least 1 order of heparin during the study period of May 1, 2009, through May 1, 2010, were included in the analysis. Subjects excluded included those whose medical records were illegibly written or incomplete (outstanding information on demographic data, current diagnosis, description of treatment, duration of hospitalization and/or treatment, treatment outcome) or those who were pregnant or breast-feeding. All patients were followed up until their discharge from the hospital to ensure a full picture of their treatment process and corresponding treatment outcomes.

Study Plan

The following data were collected from inpatient medical records and used for further analysis:

- demographic data (age and gender)
- duration of hospitalization at the inpatient setting
- treatment indication
- relative contraindications and their documentation in medical records
- data about UFH or LMWH orders (heparin name, dosage, pharmaceutical form, duration of treatment)
- monitoring of safety parameters
- treatment outcomes (assessed and classified as recovered, not recovered, recovered with sequel, death)
- ADR incidences and their reporting patterns (ADR identification, monitoring, reporting to medical records and national authorities, and follow-up)

Safety Assessments

Safety assessments were defined as the identification and reporting of ADRs. The following ADRs were analyzed in this research: coagulation abnormalities, renal dysfunction, thrombocytopenia, thrombocytosis, hyperkalemia, hematoma, anaphylactic reaction, headache/dizziness. ADR selection was based on the European Medicines Agency (EMA) Guideline on Similar Biological Medicinal Products Containing Low-Molecular-Weight Heparin, issued in April 2008. According to the World Health Organization’s Adverse Reaction Terminology, an adverse drug reaction is defined as an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, alteration of the dosage regimen, or withdrawal of the product. In other words, it is an unexpected or dangerous reaction to a drug or an unwanted effect caused by the administration of a drug.
Adherence to Heparin Use and Monitoring Guidelines

Heparin order records were compared with the monitoring standards/guidelines recommended by the EMA Guideline on Similar Biological Medicinal Products Containing Low-Molecular-Weight Heparin and Clinical Guideline for the Use and Monitoring of Low-Molecular-Weight Heparins in Community Hospitals and Community Settings. The following parameters were evaluated and compared: history of bleeding, acute peptic symptoms or other contraindications, concomitant use of drugs that may prolong bleeding time or affect platelet function, patients’ weight, and obligatory laboratory tests before administration and during the therapy.

Statistical Analysis

Microsoft Office Excel 2007 (www.microsoft.com) was used to arrange data and IBM SPSS Statistics (Statistical Package for the Social Sciences) version 18.0 (www.ibm.com/software/analytics/spss/) was used to perform statistical analyses. We determined the relationships between patient variables and the probability of any monitoring in univariable analyses and then entered the baseline characteristics that were statistically significant at the P<0.05 level. Descriptive statistics involved the estimations of average/mean/median values (± standard deviation [SD]) and the 95% confidence interval (CI). Spearman’s rank correlation coefficient (r_s) and Pearson’s chi-squared test (\chi^2) were used to evaluate correlations between the particular groups of variables. The following variables were used to conduct statistical analysis: demographic data (subjects’ age and gender), heparin name, treatment indication, dosage, duration of treatment, duration of hospitalization, safety monitoring before heparin administration, safety monitoring during the treatment course, safety monitoring after the treatment course, and treatment outcomes.

Results

Demographic Data and General Administration Trends

Three hundred and thirty-nine patients, including 177 males (52.2%) and 162 females (47.8%) with a mean age of 69.6 years, who were prescribed at least a single dose of LMWH or UFH during their stay in the hospital, were included in the study. The mean duration of hospitalization was 9.6 days (SD±9.1), and median duration of hospitalization was 8.0 days. A short-term hospital stay (fewer than 4 days) was the most frequently reported length of hospital stay in our study. The duration of hospitalization for 91 patients (26.9%) exceeded 10 calendar days; the duration of hospitalization for 101 patients (29.8%) was shorter than 6 days; and the duration of 6 to 10 days was applicable for 147 patients (43.4%). There were a few extraordinarily long stays identified. Six patients remained in the hospital for longer than 40 calendar days. Thirty-nine patients (11.5%) had long-term hospitalizations that exceeded 15 days (Table 1).

Data from the patients’ medical records showed that the most frequent indications were prophylaxis or treatment of unstable coronary artery disease (UCAD) or myocardial infarction (MI; n=166 patients, 49%) and prophylaxis of venous thromboembolism (VT) in surgery (n=135 patients, 39%). Other indications were represented by a significantly lower number of patients, including deep venous thromboembolism (DVT) in 14 patients (4.1%) and bedridden patient prophylaxis in 22 patients (6.5%; Table 2).

Safety Assessment

The following variables were analyzed against heparin safety measures: gender and age of subjects, hospital department, duration of exposure to heparin, heparin name used for the treatment, relative contraindications, and coadministration of medicines that must be coprescribed with caution. Safety data review was conducted in the following sequence in order to evaluate heparin safety monitoring patterns at the inpatient setting. Initially, all patients for whom no safety monitoring was conducted during their hospitalization period were separated from the entire sample. Then all subjects for whom safety monitoring had been performed were divided into 2 groups. Safety monitoring was performed for the first group of patients, even though no discrepancies had been identified or reported. For the second group of patients, safety monitoring was performed either as a result of various discrepancies/abnormalities or because ADRs were detected and reported. ADRs developed in 75 patients (22.1%) for whom relative contraindications were not reported at the time of treatment introduction. The most common ADR was coagulation abnormality for 25 patients (7.4%) and renal dysfunction for 24 patients (7.1%; Table 3). ADR development during treatment was associated with the previously reported relative contraindications (r_s=0.261, \chi^2=45.5, P<0.0005) and with prolonged treatment with heparin (r_s=0.279 and \chi^2=74.7, P<0.0005). Subjects for whom ADRs developed during the treatment were associated with the increased risk for negative treatment outcomes (r_s=0.221, \chi^2=22.5, P<0.0005).

Gender and Age of Subjects. Gender and age were not related to the safety monitoring trends. A similar distribution of patients was reported in all gender and age groups. An almost equal number of subjects (both genders) were allocated to the...

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**TABLE 1.** General Characteristics of Study Subjects

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients included</td>
<td>339</td>
</tr>
<tr>
<td>Female</td>
<td>162 (47.8%)</td>
</tr>
<tr>
<td>Male</td>
<td>177 (52.2%)</td>
</tr>
<tr>
<td>Age in years (mean, SD)</td>
<td>69.6 (±13.3)</td>
</tr>
<tr>
<td>Duration of hospitalization in days (mean, SD)</td>
<td>9.6 (±9.1)</td>
</tr>
<tr>
<td>Duration of LMWH therapy in days (mean, SD)</td>
<td>4.3 (±4.4)</td>
</tr>
</tbody>
</table>

LMWH = low-molecular-weight heparin; SD= standard deviation.
3 groups of safety measures ($r_5=0.028, \chi^2=0.412, P<0.8$). The majority of patients was elderly, although no statistically significant differences between a subject’s age and safety monitoring trends were identified ($r_6=-0.004, \chi^2=0.008, P<0.96$).

**Dosage.** We did not perform any additional assessment of correlation between heparin daily dose and development of adverse events. During the research it was identified that only heparin standard doses (recommended in corresponding summaries of product characteristics) were used by patients. These standard doses were not adjusted as per individual subject needs (i.e., weight, age, and renal function have not been taken into consideration selecting heparin dose).

**Hospital Department.** A statistically significant difference was observed when comparing the safety monitoring trends at various departments in the inpatient settings ($r_7=0.113, \chi^2=46.1, P<0.005$). The surgery and cardiology departments did not perform any safety monitoring in 36.2% and 55.3% of the cases, respectively. However, the department of internal medicine monitored safety for all patients; consequently, the highest numbers of discrepancies and ADRs were identified in this department. Even though safety was extensively monitored by the urology department, very few ADRs were reported in the medical records.

**Duration of Exposure to Heparins.** The mean duration of exposure to heparin therapy was 4.3 days (SD±4.4). The shortest treatment period did not exceed 4 days and was applicable for 228 patients (67.3%). Seventy-three patients (21.5%) experienced a treatment period of 5 to 7 days, and only 38 patients (8.3%) were treated with heparin for a relatively long period (8 days or more). The last period also included 4 patients who were treated with heparins for 17, 25, 38, and 53 days, respectively. The duration of exposure to heparin was also considered as an important factor due to its direct impact on the ADR rate ($r_8=0.270, \chi^2=33.2, P<0.005$). This important safety reference has to be considered before deciding to prolong the utilization of heparin in the inpatient setting. In prescribing heparin for long-term use, additional efforts have to be taken to ensure proper safety monitoring and adequate follow-up/review of relevant laboratory parameters. These actions have to be taken in order to maintain the appropriate level of patient safety.

**Heparin Name Used for the Treatment.** The following heparins were prescribed for treatment or prophylaxis: enoxaparin, nadroparin, dalteparin, bemiparin, and UFH. Doses of all heparins were within the guidelines recommended by the EMA’s Summary of Product Characteristics. Dalteparin was the most frequently prescribed medicine and was used by 236 patients.

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**TABLE 2 General Overview of Heparin Used, Treatment Indications, and Hospital Departments**

<table>
<thead>
<tr>
<th>Department</th>
<th>Treatment Indications</th>
<th>DVT</th>
<th>Prophylaxis of VT in Surgery</th>
<th>Prophylaxis for Bedridden Patients</th>
<th>Treatment of UCAD or MI</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiology</td>
<td>n=0</td>
<td>n=1</td>
<td>n=0</td>
<td>n=19</td>
<td>n=0</td>
<td></td>
</tr>
<tr>
<td>Internal medicine</td>
<td>n=12</td>
<td>n=5</td>
<td>n=18</td>
<td>n=40</td>
<td>n=2</td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>n=2</td>
<td>n=80</td>
<td>n=0</td>
<td>n=2</td>
<td>n=0</td>
<td></td>
</tr>
<tr>
<td>Urology</td>
<td>n=0</td>
<td>n=49</td>
<td>n=0</td>
<td>n=0</td>
<td>n=0</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>5</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>14</td>
<td>135</td>
<td>22</td>
<td>160</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Heparin name</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Enoxaparin</td>
<td>n=0</td>
<td>n=12</td>
<td>n=0</td>
<td>n=0</td>
<td>n=0</td>
</tr>
<tr>
<td>Fraxiparin</td>
<td>n=11</td>
<td>n=61</td>
<td>n=20</td>
<td>n=144</td>
<td>n=2</td>
</tr>
<tr>
<td>Nadroparin</td>
<td>n=2</td>
<td>n=39</td>
<td>n=2</td>
<td>n=12</td>
<td>n=0</td>
</tr>
<tr>
<td>Heparin</td>
<td>n=1</td>
<td>n=0</td>
<td>n=0</td>
<td>n=9</td>
<td>n=0</td>
</tr>
<tr>
<td>Bemiparin</td>
<td>n=0</td>
<td>n=23</td>
<td>n=0</td>
<td>n=1</td>
<td>n=0</td>
</tr>
<tr>
<td>Total</td>
<td>14</td>
<td>135</td>
<td>22</td>
<td>160</td>
<td>2</td>
</tr>
</tbody>
</table>

* DVT = deep venous thrombosis; MI = myocardial infarction; UCAD = unstable coronary artery disease; VT = venous thrombosis.
Influence of Coadministration of Antithrombotic Medicines, Warfarin, and NSAIDs on Heparin Safety: Data from a Prospective Observational Study

TABLE 3 Adverse Drug Reactions and Their Incidence Rates

<table>
<thead>
<tr>
<th>Adverse Drug Reaction</th>
<th>Frequency</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coagulation abnormalities*</td>
<td>25</td>
<td>7.37</td>
</tr>
<tr>
<td>(PT outside 70%-100% range and/or APTT outside 35-50s range and/or INR outside 0.8-1.2 range)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal dysfunction*</td>
<td>24</td>
<td>7.08</td>
</tr>
<tr>
<td>(Creatinine outside 70-132 micromoles per liter range and/or urea outside 1.7-8.3 millimoles per liter range)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia*</td>
<td>10</td>
<td>2.95</td>
</tr>
<tr>
<td>(PLT count &lt;100×10^9 per liter)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombocytosis*</td>
<td>8</td>
<td>2.10</td>
</tr>
<tr>
<td>(PLT count &gt;450×10^9 per liter)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperkalemia*</td>
<td>4</td>
<td>1.18</td>
</tr>
<tr>
<td>(Potassium level &gt;5.5 millimoles per liter)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematoma (bleeding)</td>
<td>2</td>
<td>0.60</td>
</tr>
<tr>
<td>Anaphylactic reaction</td>
<td>1</td>
<td>0.30</td>
</tr>
<tr>
<td>Headache/dizziness</td>
<td>1</td>
<td>0.30</td>
</tr>
<tr>
<td>Total</td>
<td>75</td>
<td>—</td>
</tr>
</tbody>
</table>

*All laboratory tests of interest were performed at the local lab in the corresponding clinical hospital. Automated methods were used to analyze lab samples. APTT = activated partial thromboplastin time; INR = international normalized ratio; PLT = platelet; PT = prothrombin time.

(69.6%). The second- and third-most prescribed LMWHs were nadroparin (n = 55, 16.2%) and bemiparin (n = 24, 7.1%). Orders of other heparins did not exceed 4%. ADR development during the treatment was not associated with the type of the heparin used ($r_s = -0.044$, $\chi^2 = 13.6$, $P < 0.09$).

Relative Contraindications. Relative contraindications were reported for 256 patients (75.5%). The most frequently reported relative contraindication for the use of heparin was age (n = 234, 69%), followed by coagulation abnormalities (n = 92, 24.3%) and renal dysfunction (n = 41, 10.9%). One hundred and seventy-six patients (51.9%) had only 1 relative contraindication, while 50 patients (14.8%) had 2 relative contraindications, and 30 patients (8.9%) were identified with 3 or more relative contraindications. Corresponding dose adjustments were not reported for any of the patients having relative contraindications, and a standard dose of UFH or LMWH was used for these patients (Table 4).

Based on study results, patients with relative contraindications were associated with an increased risk for prolonged treatment with heparin ($r_s = 0.286$, $\chi^2 = 69.3$, $P < 0.0005$), an increased risk for the development of ADRs ($r_s = 0.277$, $\chi^2 = 17.5$, $P < 0.0005$), an increased risk for negative treatment outcomes ($r_s = 0.236$, $\chi^2 = 50.5$, $P < 0.0005$), and an increased risk for a prolonged hospitalization period ($r_s = 0.169$, $\chi^2 = 11.6$, $P < 0.003$).

Coadministration of Medicines That Have to be Prescribed with Caution. Based on products’ summary characteristics data, due to increased risk of bleeding, LMWHs should be used with caution in patients receiving oral anticoagulants, platelet inhibitors, NSAIDs, and thrombolytics (Table 5). We identified only concomitant use of acetylsalicylic acid, clopido- grel, NSAIDs, and warfarin together with heparins in patient records. In cases where coadministration of LMWHs with these agents is necessary, it is advise to implement close clinical and laboratory monitoring of these patients (Table 6).

Subjects for whom warfarin, acetylsalicylic acid, clopido- grel, ketorolac, and NSAIDs were prescribed during the treatment phase were associated with an increased risk for the development of ADRs. The relationship was low but statistically significant. The strongest relationship was with the coadministration of acetylsalicylic acid ($r_s = 0.283$, $\chi^2 = 21.42$, $P < 0.0005$), while the coadministration of NSAIDs had only a very weak relationship to the development of ADRs ($r_s = 0.133$, $\chi^2 = 21.01$, $P < 0.0005$). Data are presented in Table 7.

Patients for whom warfarin, acetylsalicylic acid, clopido- grel, ketorolac, and NSAIDs were prescribed during the treatment phase showed an increased risk for the development of thrombocytopenia; the strongest risk was calculated for coad-

TABLE 4 Relative Contraindications and Their Incidence Rates

<table>
<thead>
<tr>
<th>Relative Contraindication</th>
<th>Identified Before Treatment Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency (%)</td>
<td></td>
</tr>
<tr>
<td>Age (&gt;65 years)</td>
<td>234 (69.0)</td>
</tr>
<tr>
<td>Coagulation abnormalities*</td>
<td>92 (24.3)</td>
</tr>
<tr>
<td>(PT outside 70%-100% range and/or APTT outside 35-50s range and/or INR outside 0.8-1.2 range)</td>
<td></td>
</tr>
<tr>
<td>Renal dysfunction*</td>
<td>41 (10.9)</td>
</tr>
<tr>
<td>(Creatinine outside 70-132 micromoles per liter range and/or urea outside 1.7-8.3 millimoles per liter range)</td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia*</td>
<td>18 (4.7)</td>
</tr>
<tr>
<td>(PLT count &lt;100×10^9 per liter)</td>
<td></td>
</tr>
<tr>
<td>Thrombocytosis*</td>
<td>10 (2.6)</td>
</tr>
<tr>
<td>(PLT count &gt;450×10^9 per liter)</td>
<td></td>
</tr>
<tr>
<td>Hyperkalemia*</td>
<td>11 (2.9)</td>
</tr>
<tr>
<td>(Potassium level &gt;5.5 millimoles per liter)</td>
<td></td>
</tr>
</tbody>
</table>

*All laboratory tests of interest were performed at the local lab in the corresponding clinical hospital. Automated methods were used to analyze lab samples. APTT = activated partial thromboplastin time; INR = international normalized ratio; PLT = platelet; PT = prothrombin time.

TABLE 5 Medicines to be Coprescribed with Caution with Low-Molecular-Weight Heparin

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>List of Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticoagulants</td>
<td>Warfarin,acenocoumarol</td>
</tr>
<tr>
<td>Platelet inhibitors</td>
<td>Acetylsalicylic acid, salicylates, ticlopidine, clopidogrel</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>Ketorolac tromethamine, dipyriramole, sulfinpyrazone</td>
</tr>
<tr>
<td>Thrombolytics</td>
<td>Streptokinase, alteplase</td>
</tr>
<tr>
<td>NSAID = nonsteroidal anti-inflammatory drug</td>
<td></td>
</tr>
</tbody>
</table>
ministration of warfarin ($r_s = 0.248, \chi^2 = 28.14, P < 0.0005$, Table 7), while coadministration of medicines from the list did not have a relationship to the risk of thrombocytosis (Table 7). We were unable to evaluate coadministration of medicines and the risk of bleeding due to a small number of patients suffering from bleeding as an ADR.

**Discussion**

Our analysis of heparin’s utilization worldwide suggested that its use in clinical practice has increased significantly recently and Lithuanian utilization data shows the same utilization trends. The use of LMWH in Lithuania has increased from 40.12 DDDs per 1,000 inhabitants in 2003 to 272.75 DDDs per 1,000 inhabitants in 2010. Utilization studies of LMWH in other countries have reported a similar increase in use. For example, during the period 2001-2010, Croatia reported an increase in expenditure on heparin treatment from $11.4 to $38.5 million and an increase in utilization from 0.42 DDD per 1,000 inhabitants to 1.96 DDD per 1,000 inhabitants—4.66 times more. A study of medication utilization patterns in a tertiary care university hospital in Israel conducted in 2007-2008 showed that the various heparins were the most frequently prescribed drugs at their admission units; 2,102 DDDs were prescribed during the most recent 6 months of investigation. In general, this corresponded to an average of almost 10 DDDs of heparin being utilized by each individual patient during his or her hospital stay. Thus, the monitoring of rational and safe use of LMWH is essential in clinical practice.

**Evaluation of Safety**

Meta-analysis of comparative evaluations of UFH and LMWHs have revealed reductions in safety and efficacy of 30% to 40% in favor of LMWHs, with no conclusive evidence that LMWHs have intrinsically different safety and/or efficacy profiles. Furthermore, it is quite likely that these differences are related to, or are the direct result of, the markedly variable manufacturing strategies employed to produce each LMWH. There are no data, however, to suggest that these variable pharmacodynamic or pharmacologic properties translate into differences in clinical outcomes or safety. Consequently, the only conclusion supported by these observations is that these LMWHs are essentially the same in treatment or prevention at the dosages used in clinical trials.

The ESCAPE-END study (Efficacy, Safety, Cost-effectiveness and Effect on PAI-1 of Enoxaparin, Nadroparin, and Dalteparin) was conducted to compare the 3 LMWHs in patients with unstable angina. Prospective, randomized, comparative, and open with blinded endpoints assessments with a 30-day follow-up (PROBE design) showed that all 3 LMWHs evaluated in this study were similar with respect to efficacy, safety, PAI levels, and cost-effectiveness.

The results of our study also supported the hypothesis that LMWHs could be interchangeable in the treatment of DVT, pulmonary embolism, recurrent angina, and MI. In comparison to UFH, all LMWHs have independently demonstrated greater safety and effectiveness. None of the LMWHs demonstrated a significant superiority over another; therefore, the group of LMWHs could be interchangeable for the indications stated above in terms of safety and effectiveness.

**Safety Monitoring Adherence to Heparin Use and Monitoring Guidelines**

The results of our study confirmed low adherence to LMWH safety monitoring guidelines in local Lithuanian hospitals in comparison with international standards. The periodic

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**TABLE 6** Frequency of Medicines to be Prescribed with Caution with Low-Molecular-Weight Heparin

<table>
<thead>
<tr>
<th>Name of Agent Prescribed with Precaution</th>
<th>Frequency</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin</td>
<td>5</td>
<td>1.47</td>
</tr>
<tr>
<td>Acetylsalicylic acid</td>
<td>115</td>
<td>33.92</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>13</td>
<td>3.83</td>
</tr>
<tr>
<td>Ketorolac</td>
<td>89</td>
<td>26.25</td>
</tr>
<tr>
<td>Other NSAIDs</td>
<td>40</td>
<td>11.80</td>
</tr>
</tbody>
</table>

**TABLE 7** Concomitant Use of Medicines with Caution and Increased Risk of Adverse Drug Reactions, Thrombocytopenia, and Thrombocytosis

<table>
<thead>
<tr>
<th>Name of Agent</th>
<th>( r_s )</th>
<th>( \chi^2 )</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetylsalicylic acid</td>
<td>0.283</td>
<td>21.42</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>Ketorolac</td>
<td>0.272</td>
<td>27.16</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>Warfarin</td>
<td>0.249</td>
<td>27.16</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>0.203</td>
<td>19.29</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>0.133</td>
<td>21.01</td>
<td>&lt;0.0005</td>
</tr>
</tbody>
</table>

**TABLE 8** Concomitant Use of Medicines with Caution and Increased Risk of Adverse Drug Reactions

<table>
<thead>
<tr>
<th>Name of Agent</th>
<th>( r_s )</th>
<th>( \chi^2 )</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetylsalicylic acid</td>
<td>0.238</td>
<td>20.24</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>Ketorolac</td>
<td>0.188</td>
<td>20.61</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>0.114</td>
<td>18.92</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>0.101</td>
<td>11.10</td>
<td>&lt;0.0005</td>
</tr>
</tbody>
</table>

**NSAID = nonsteroidal anti-inflammatory drug**

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evaluation of real-life practices may improve adherence to guidelines and potentially improve clinical outcomes. Underdosing can lead to lack of efficacy and new thromboembolic events during hospitalization, while overdosing often leads to an increase in ADRs. Thus, the rational dose of LMWH for a patient should be calculated based on a patient’s age, weight, and renal function.

Despite the fact that monitoring is beneficial, many publications have cited very low monitoring of heparin effectiveness and safety in different countries. The United Kingdom’s (UK) National Patient Safety Agency (NPSA) reported LMWH dosing errors and evidence of harm. Between January 2005 and September 2009, the NPSA received 2,716 patient safety incident reports related to LMWH use, including include 1 incident that led to death and 3 reports of severe harm to patients. Reports of the UK National Reporting and Learning System (NRLS) indicate that some patients are not weighed prior to administration, that the body weight is estimated or recorded inaccurately, or that doses based on a patient’s weight are misclassified. These documents reported numerous incidents in which the prescribed, dispensed, or administered dose and frequency of LMWH were outside the accepted guidelines and did not account for other predisposing conditions such as renal failure. Limited patient information (i.e., weight, dose, indication, and intended duration of treatment) communicated at transfers of care has also led to reports of harm.

In response to the NPSA alert, the Thrombosis Committee at the Barnet and Chase Farm Hospitals (BCFH) in the UK performed an audit of LMWH prescriptions at the hospitals. The audit covered 47 surgical and medical patients treated at BCFH during the period January 2-February 3, 2012. According to the audit findings, the body weight of 51.1% of patients was not documented in the bedside folders and on the inpatient charts; the renal function of 8.5% of patients was not considered after the second dose; and 26.9% of patients did not have an indication of their LMWH therapy documented on their discharge summaries, despite the fact that all 3 monitoring standards are mandatory in the hospital.

An audit of a database of patients treated with LMWH at the University Medical Center Utrecht in the Netherlands revealed low compliance with platelet count monitoring, as well as initial management of suspected heparin-induced thrombocytopenia (HIT). Assessment of LMWH use in Dutch hospitals for the treatment of acute coronary syndrome in light of the current European Society of Cardiology guidelines showed that dose adjustment of LMWH therapy for patients with renal failure is not applied in 71% of hospitals. Likewise, LMWH dose adjustment is not applied for patients aged over 75 years in 92% of hospitals. The authors have concluded that an additional benefit may be achieved by the routine dose adjustment of LMWH for patients with renal insufficiency and aged over 75 years, since these patients are at high risk of bleeding complications secondary to antithrombotic treatment. The same risk of bleeding ADR was reported in elderly patients and patients with renal failure by a prospective LMWH utilization study at the University Hospital of Toulouse, France. The authors have also concluded that more pharmacoepidemiology studies in patients with several risk factors, particularly in elderly patients and in patients with renal failure, would be useful in order to determine the optimal method of use for each LMWH.

Clinicians should include evaluations of compliance with platelet count monitoring with UFH and LMWH, as well as the appropriateness of the initial management strategies for HIT and direct thrombin inhibitor protocols in their patient safety practice assessments. Practitioners in U.S. hospitals are implementing anticoagulation dosing and monitoring protocols to improve the safety of anticoagulation therapy.

The timely, adequate, and comprehensive reporting of ADRs is an essential part of patients’ medical care, allowing the justification of future therapy alterations and helping to prevent medical inpatients from repeated ADRs during their hospital stays. A study on UFH and LMWH use in French hospitals showed that the implementation of guidelines in clinical practice has had a positive impact on medical practice, at least by improving the safety of the drugs used. A significant decrease in hemorrhagic ADRs was reported after the implementation of new guidelines on UFH and LMWH use in hospitals and changes in their use. The dosage of LMWH was adjusted more in accordance with renal function, and no ADRs were observed in patients with severe renal impairment.

As a response to the low monitoring of LMWH effectiveness and safety, health care providers have started to implement clinical guidelines regarding the use and monitoring of LMWH in community hospitals and community settings. The guidelines are designed to provide information to support the staff on the safe and appropriate use and monitoring of LMWH across secondary and primary care units and to reduce dosage errors when prescribing it.

Limitations
Our study has several limitations. This research was conducted at 1 of the secondary-level clinical hospitals in the country; thus, some variation might occur in similar investigations conducted at other health care facilities due to variation in local practices. Also, all data have been collected manually, since there are no unified orders or dispensing databases available in hospitals in Lithuania. Some of the study results were considered as not statistically significant mainly due to the variation of patients’ distribution in the selected treatment groups.

Conclusions
It is essential to emphasize the importance of safety monitoring in patients when administering heparin. In particular, it is necessary to closely monitor patients with relative
contraindications; patients to whom heparins are prescribed for a long-term treatment; and patients with concomitant use of antithrombotic medicines, NSAIDs, and warfarin due to increased risk of ADRs. Low-molecular-weight heparins did not differ in terms of their safety parameters; therefore, the requirement for additional follow-up was not affected by the heparin brand or name prescribed for each patient. The study results highlight some gaps in the documentation of information regarding the use of LMWH. A particular weakness was found in the recording and communication of information; thus, the implementation of national guidelines on the use of LMWH is preferable.

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DISCLOSURES

The authors report no financial conflicts of interest related to the subjects discussed in this article.

Concept, design, data collection, data analysis, and manuscript writing were performed by all authors.

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The *Journal of Managed Care Pharmacy* would like to thank the 177 reviewers who have reviewed manuscripts in the first 5 months of 2013 and contributed to the high quality of articles in *JMCP*. This reviewer participation rate is an 80% increase over the same period in 2011 or 2012. Without this excellent level of reviewer involvement, *JMCP* would not be the fine scholarly publication where readers come for cutting edge managed care research.

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