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

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In 1990, Robert was the director of pharmacy at Health Net. The following year, HealthNet and the managed care industry was in the news because HealthNet denied payment for what was considered by some at the time to be a non-evidence-based experimental bone marrow transplant treatment for a patient with breast cancer to enable her to receive more chemotherapy. The patient died, and in 1993, the jury awarded the family $89.1 million, the largest settlement of its kind to that date in a landmark case. Evidence-based medicine and cost control were on trial, and some would argue that they lost, leading to increased health care costs and more expensive aggressive cancer therapy. Robert is now clinical professor at the University of Florida College of Pharmacy and enjoys his teaching, research, and service responsibilities. He is also president of NavarroPharma, where he continues his consulting practice.

Pete was the director of pharmacy at Group Health of Puget Sound, one of the largest staff-model health maintenance organizations in the United States, serving 500,000 members. Group Health was known for high-quality, cost-effective care; for its leadership in adopting, applying, and promoting evidence-based medicine; for being one of the earliest organizations to computerize the pharmacy program; and for its rigorous pharmacy and therapeutics processes. The critical issues he faced at Group Health were managing cost and quality. Pete is now involved with managed care pharmacy through his company, Formulary Resources, LLC, where he serves as president.

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Dear JMCP readers,

It is an honor to be asked to serve as editor-in-chief of JMCP as AMCP enters its milestone 25th anniversary. I remember when JMCP was making its debut as a journal in the summer of 1995, during the presidency of Jay Messeroff and with Louise J. Sargent as editor-in-chief. JMCP was born after many months of planning by a committee that included Shawn Burke, Grace Fong, John Hopkins, Dennis Houghton, Scott Larson, Ellen Osborne, Suzanne Rivkin, Louise Sargent, and William Tindall. The mission of JMCP outlined in that first issue has remained essentially unchanged, a testament to the well-conceived vision of the founders:

JMCP, as the official journal of the Academy of Managed Care Pharmacy, provides applied, professional, and scientific information to advance pharmacy’s contribution to patient care in managed health care systems.

Under the leadership of JMCP’s past editors—Louise Sargent, Michael Posey, Craig Stern, Fred Curtiss, and Robert Navarro—the journal continuously improved its ability to bring leading-edge practice initiatives, original research, and commentary to AMCP members and others in the managed care community. It has seen steady improvement in its SCI Impact Factor score, which is a measure of its impact on current research publication activity. JMCP has recently been ranked at the top of all pharmacy professional journals. Yet we all know that now is not the time to rest on past accomplishments. We must continue to improve through the next 25 years of AMCP history—and beyond.

As editor of JMCP, I will work to continue to keep the journal at the cutting edge. On this issue’s cover, articles are being classified as Benefit Management (a historic underpinning of managed care practice) and Clinical Management (reflecting the growing use of guidelines and algorithms to improve outcomes). While these two activities must be conducted simultaneously in managed care organizations, articles may give greater emphasis to one form of management over the other. JMCP will also be featuring articles describing the use of economic models that are used to estimate the potential to improve outcomes and/or lower costs. Because the health care system in which we operate will continue to see change, I am actively soliciting articles on health policy issues and initiatives (ACOs, HIT, CER, meaningful use, etc.) so that readers are in a better position to shape the future of health care, instead of being shaped by it.

The very method used by medical journals to collect and disseminate cutting-edge knowledge will also continue to change, and JMCP plans to be a leader in those methods. The systems we use to accept, review, and publish articles will have to deliver faster and higher-quality manuscripts. Currently, the journal has an open-access policy, where anyone can download copies of past articles for their personal use without charge. Our web-based access (direct to PubMed) has been increasing annually, and we expect that use will accelerate as the need for the most current information increases. We will have the capability to offer more than just copies of articles on the JMCP web site and will be incorporating those forms of information transfer. Webinars and other interactive forums are being considered to keep JMCP at the cutting edge of journals.

I was attracted to the JMCP editor position because I believe in the value of learning and discovery. Thirty-five years ago, I sat in a pharmacy school class room at the University of Illinois learning about health maintenance organizations and how they could reduce health care costs and improve outcomes. Almost 30 years ago, I was teaching pharmacy students at the University of North Carolina about the rapidly growing health care costs and how policy initiatives have been tried to improve outcomes and lower costs but that few live up to their promise. I then continued learning, discovering, and teaching while I worked at Glaxo, and we experimented with new ways to assess the value of pharmaceuticals and to implement disease management programs. During that time, I had the opportunity to work with many AMCP past presidents, leaders, and their staff (Hank Blissenbach at DPS, Perry Cohen at Aetna, John Chiufo at Pilgrim, Diane Giaquinta at WellPoint, Jay Messeroff at HIP, Robert Navarro at HealthNet, Pete Penna at Group Health, and many others). All of them were blazing new trails as they implemented programs to improve outcomes and lower costs in their populations. Working with these leaders and visionaries fuels one’s desire for further discovery. Most recently, I have been developing outcomes-related products and solutions through my own company, Center for Outcomes Research.

All those experiences have taken me down the path to this opportunity as editor of JMCP, where I hope to share my love for learning and discovery and to give others the opportunity to share what they have learned and discovered along their path in managed care. While many trails have been cleared by those who came before us, the landscape is constantly changing, and new solutions are yet to be discovered and shared in JMCP. I look forward to working with you.

Your editor,

John Mackowiak, PhD
Editor-in-Chief, JMCP
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JMCP abstracts should be carefully written narratives that contain all of the principal quantitative and qualitative findings, with the outcomes of statistical tests of comparisons where appropriate. Abstracts are required for all manuscript submissions except Commentaries and Letters. The format for the abstract is Background, Objective, Methods, Results, Conclusion.

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- A subsection in the Discussion labeled “Limitations” is required for all articles except Commentaries and Letters.
- Most articles should incorporate or at least acknowledge the relevant work of others published previously in JMCP (see “Article Index by Subject Category” at www.amcp.org/JMCPhome.aspx).
- Product trade names may be used only once for the purpose of providing clarity for readers, generally at the first citation of the generic name in the article but not in the abstract.
- Many articles include research that may pose a threat to either patient safety or privacy. It is the responsibility of the principal author to ensure that the manuscript is submitted with either the result of review by the appropriate institutional review board (IRB) or a statement of why the research is exempt from IRB review (see “Policy for Protecting Patient Safety and Privacy” at www.amcp.org/JMCPhome.aspx).

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References should be prepared following modified AMA style. All reference numbers in the manuscript should be superscript (e.g., 1). Each unique reference should have only one reference number. If that reference is cited more than once in the manuscript, the same number should be used. Do not use ibid or op cit for JMCP references. Please provide Web (hyperlink) addresses for all free access references. An access date should be included for every URL except links to JMCP articles. See examples 2 and 3 in the second column. Here are examples of the style format for common types of references:


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REFERENCE

A Markov Model of the Cost-Effectiveness of Pharmacist Care for Diabetes in Prevention of Cardiovascular Diseases: Evidence from Kaiser Permanente Northern California

Junhua Yu, PhD, MS; Bijal M. Shah, PhD; Eric J. Ip, PharmD, BCPS, CSCS, CDE; and James Chan, PharmD, PhD

ABSTRACT

BACKGROUND: It has been demonstrated in previous studies that pharmacist management of patients with type 2 diabetes mellitus (T2DM) in the outpatient setting not only improves diabetes-related clinical outcomes such as hemoglobin A1c but also blood pressure (BP), total cholesterol (TC), and quality of life. Improved control of BP and TC has been shown to reduce the risks of cardiovascular disease (CVD), which has placed a heavy economic burden on the health care system. However, no study has evaluated the cost-effectiveness of pharmacist intervention programs with respect to the long-term preventive effects on CVD outcomes among T2DM patients.

OBJECTIVES: To (a) quantify the long-term preventive effects of pharmacist intervention on CVD outcomes among T2DM patients using evidence from a matched cohort study in the outpatient primary care setting and (b) assess the relative cost-effectiveness of adding a clinical pharmacist to the primary care team for the management of patients with T2DM based on improvement in CVD risks with the aid of an economic model.

METHODS: Clinical data between the periods of June 2007 to February 2010 were collected from electronic medical records at 2 separate clinics at Kaiser Permanente (KP) Northern California, 1 with primary care physicians only (control group) and the other with the addition of a pharmacist (enhanced care group). Patients in the enhanced care group were matched 1:1 with patients in the control group according to baseline characteristics that included age, gender, A1c, and Charlson comorbidity score. The estimated 10-year CVD risk for both groups was calculated by the United Kingdom Prospective Diabetes Study (UKPDS) Risk Engine (version 2) based on age, sex, race, smoking status, atrial fibrillation, duration of diabetes, levels of A1c, systolic BP (SBP) and TC, and high-density lipoprotein cholesterol (HDL-C) observed at 12 months. There was no statistical difference in the baseline clinical inputs to the Risk Engine (A1c \( P = 0.115 \), SBP \( P = 0.184 \), TC \( P = 0.055 \), and HDL-C \( P = 0.475 \)) between the 2 groups. A Markov model was developed to simulate the estimated CVD outcomes over 10 years and to estimate cost-effectiveness. The final outcomes examined included incremental cost and effectiveness measured by life years, incremental quality-adjusted life year gained. Both deterministic and probabilistic SA were conducted to examine the robustness of the results.

RESULTS: The estimated risks for coronary heart disease (CHD) and stroke (both nonfatal and fatal) at the end of the follow-up period in the enhanced care group compared with the control group were similar. The absolute risk reduction (ARR) between the enhanced care and control groups increased over time. For example, the ARR for nonfatal CHD risk in year 1 was 0.5% (1.2% vs. 0.7%), whereas the ARR increased to 5.5% in year 10 (14.8% vs. 9.3%). Similarly, the ARR between the enhanced care and control groups was calculated as 0.3% for fatal CHD in year 1 and increased to 4.6% in year 10. Results from the Markov model suggest that the enhanced care group was shown to be a dominant strategy (less expensive and more effective) compared with the control group in the 10-year evaluation period in the base-case (average or mean results) scenario. Sensitivity analysis that took into account the uncertainty in all important variables, such as wage of pharmacists, utility weight (the degree of preference individuals have for a particular health state or condition), response rate to pharmacists’ care, and uncertainty associated with the estimated 10 years of CVD risk, revealed that the relative value of enhanced care was robust to most of the variations in these parameters. Notably, the level of cost-effectiveness measured by net monetary value depends on the time horizon adopted by the payers and the magnitude of CVD risk reduction. The enhanced care group has a higher chance of being considered as a cost-effective strategy when a longer time horizon such as a minimum of 4 to 5 years is adopted.

CONCLUSIONS: Adding pharmacists to the health care management team for diabetic patients improves the long-term CVD risks. The longer-term CVD risk reductions were shown to be more dramatic than the short-term reduction. A longer time horizon adopted by health plans in managing T2DM patients has a higher probability of making the intervention cost-effective.

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What is already known about this subject

• The economic burden associated with cardiovascular disease (CVD) complications among type 2 diabetes mellitus (T2DM) patients is substantial. Adults with diabetes are 2-4 times more likely to have heart disease or stroke, and the total direct medical care costs for treating 1 typical established CVD patient can be $18,953 per year.
• Pharmacist management of patients with T2DM in the outpatient setting not only improves diabetes-related clinical outcomes such as hemoglobin A1c but also the secondary outcomes such as blood pressure (BP) and cholesterol levels, which are highly predictive of CVD risks.
• Pharmacist disease management programs have been shown to be cost-effective when considering labor and program costs. However, no studies have evaluated the cost-effectiveness of pharmacist intervention programs with respect to the long-term CVD outcomes among T2DM patients using a rigorous modeling approach.
What this study adds

- The estimated long-term risks for coronary heart disease (CHD) and stroke (both nonfatal and fatal) at the end of follow-up were consistently lower in the enhanced care group compared with the control group, even though baseline risks in both groups were similar.
- The absolute risk reduction (ARR) between the enhanced care and control groups increased over time. For example, the ARR in the nonfatal CHD risk in year 1 was 0.5% (1.2% vs. 0.7%), whereas the ARR increased to 5.5% in year 10 (14.8% vs. 9.3%). Similarly, the ARR between the enhanced care and the control groups was calculated as 0.3% for fatal CHD in year 1 and increased to 4.6% in year 10.
- The Markov model constructed using data from a matched cohort study demonstrated that the enhanced care group dominated the control group with lower treatment cost ($35,740 vs. $44,528) per patient and more life years (8.9 vs. 8.1 years) and quality-adjusted life-years (QALY, 5.51 vs. 5.02 years) over the 10-year period.
- The results were robust to almost all possible variations of the relevant parameters in the model except for the time horizon of the health plan. Based on our research, if health plans were willing to pay $50,000/QALY, it would take at least 4-5 years for the addition of clinical pharmacists to the health care team to be cost-effective without any uncertainty.

Type 2 diabetes mellitus (T2DM) is an independent risk factor for cardiovascular disease (CVD) and is increasingly being recognized as a controllable risk factor. Adults with diabetes are 2-4 times more likely to have a heart disease or a stroke, which is the cause of death in at least 65% of these patients. The total direct medical care costs for treating an established CVD patient can be $18,953 per year. In particular, the costs for patients who experience a secondary CVD hospitalization are 4.5 times higher compared with those who avoid subsequent inpatient stays. Thus, a large proportion of the economic burden of T2DM can be attributed to cardiovascular complications, and substantial cost savings can be achieved through effective prevention of CVD.

Pharmacist care for T2DM patients can be instrumental in the prevention of CVD. It has been demonstrated in numerous studies that pharmacist management of patients with T2DM in the outpatient setting can improve glycemic levels such as hemoglobin A1c along with blood pressure (BP), cholesterol levels, and overall quality of life (QOL). Since BP and cholesterol levels are significant predictors of long-term macrovascular disease such as coronary artery disease, stroke, and peripheral vascular disease, better control of these clinical markers would presumably decrease CVD risk among diabetic patients. The intervention we attempted to evaluate in this study was conducted in Kaiser Permanente (KP) Northern California. A team of 16 primary care physicians (PCPs) in the Internal Medicine Department referred their diabetic patients with poor glycemic control (i.e., Alc >7%) to the clinical pharmacist for more stringent control and medical follow-up. The pharmacist managing patients in this study was clinically trained, having completed a Doctor of Pharmacy (PharmD) degree and a 1-year post-doctoral pharmacy residency and having earned a Certified Diabetes Educator credential. The pharmacist prescribed and adjusted medications, ordered laboratory work, ordered and administered immunizations, provided diabetes self-management education, and worked to optimize overall glycemic and cardiovascular care of patients. The study found that in the enhanced care group the mean Alc decreased from 9.5% to 6.9% compared with 9.3% to 8.4% in the control group ($P<0.001$) after 12 months. Compared with the control group, the enhanced care group increased the probability of achieving an Alc <7% (odds ratio (OR) 3.9, $P<0.001$), low-density lipoprotein cholesterol (LDL-C) <100 milligrams per deciliter (mg/dL; OR 2.0, $P=0.0152$), BP <130/80 millimeter of mercury (mmHg; OR 2.0, $P=0.0016$), and all 3 goals simultaneously (OR 3.2, $P=0.0004$). The 10-year coronary heart disease (CHD) risk decreased from 16.4% to 9.3% in the enhanced care group compared with 17.4% to 14.8% in the control group ($P<0.001$).

Given the clinical benefits of pharmacist intervention programs for diabetic patients, it is important to quantify their economic value in controlling long-term CVD risk factors from the payer perspective. Two studies have explored the economic impact of pharmacist interventions in managing diabetic patients. However, further data are needed to expand the literature to document the preventive outcomes of CVD risks and address methodological issues posed by the existing literature.

The Asheville Project was one of the first large-scale studies to document the positive impact of a pharmacist-run diabetes management program on clinical and economic outcomes in the community pharmacy setting. More recently, the Diabetes Ten City Challenge reported similar results. Although both studies attempted to assess the economic outcomes of pharmacist intervention, they relied on evidence collected from community pharmacy settings in geographically distinct locations. Furthermore, both studies utilized outcomes measured using a pre-/post-comparison study design without using a concurrent control group. This study design has 2 main disadvantages: inability to control for confounding factors changing over the follow-up period and regression to the mean—both of which may bias the study outcomes. In addition, of the 2 economic studies available (with a control group), only 1 evaluated pharmacist care in the outpatient setting; however, it was limited by documenting only program characteristics and labor costs. In summary, previous economic evaluations have the drawbacks of either relying on evidence lacking generalizability or...
omitting economic costs relevant to payers. Most importantly, none of these studies evaluated the cost-effectiveness of pharmacist intervention programs with respect to the long-term CVD outcomes among T2DM patients using a rigorous modeling approach. The need for data on long-term effectiveness of treatment strategies among diabetic patients has long been recognized.\textsuperscript{13}

Therefore, the overall goals of this study are to (a) quantify the long-term preventive effects of pharmacist intervention on CVD outcomes among T2DM patients using evidence from a matched cohort study in the outpatient primary care setting and (b) assess the relative cost-effectiveness of adding a clinical pharmacist to the primary care team for the management of patients with T2DM based on improvement in estimated CVD risks with the aid of an economic model.

**Methods**

**Model Overview**

A Markov model with 1-year cycles was developed to simulate CVD events and death risk for 2 hypothetical cohorts of patients: (1) the enhanced care group where patients were managed by a clinical pharmacist who was integrated as part of the primary care team as a provider and (2) the control group where patients received only the usual care of primary care physicians (PCPs). Figure 1 depicts a simplified presentation of the model.\textsuperscript{14} Patients in both arms entered the model through the “well” state. As patients aged during the 10-year simulation, they could remain free of events, develop a first CHD or stroke, develop recurrent CHD or stroke (either fatal or nonfatal), or die from the events or other natural causes in any model cycle. We assumed that patients who had experienced a first CHD event or stroke would continue to be exposed to the risk for subsequent strokes or CHD events, with a maximum of 3 nonfatal events (1 stroke and 2 CHD, 2 strokes and 1 CHD, 3 CHD or 3 strokes).\textsuperscript{14} This model was a Markov model with 11 mutually exclusive health states to take into account various combinations of a maximum total of 3 strokes and CHD events (well, free of history of events, survival from primary stroke, survival from second stroke, survival from third stroke, survival from primary CHD, survival from second CHD, survival from third CHD, survival from CHD once and stroke once, survival from CHD twice [once] and stroke once [twice], event death, and other death). Based on the total time spent in the different health states, the model estimated the expected survival for patients in each treatment arm, and it was combined with cost and quality of life (QOL) data to estimate the relative cost-effectiveness. It is worth noting that stroke and CHD had differing impacts on the utility and costs accumulated over the time horizon of the model. The utility reduction for stroke was different than that for CHD; in addition, the treatment costs for CHD and stroke also varied. Therefore, it was important to have different health states to identify the exact type of events and the number of events from the point of view of calculation. For example, once patients entered the health state of survival of primary nonfatal CHD, there were 6 possibilities of transitions in the next cycle: (1) transit to the state of survival from CHD once and stroke once if a nonfatal stroke happened; (2) transit to event death if a fatal stroke happened; (3) transit to survival from second CHD if a nonfatal CHD happened; (4) transit to survival of event death if a fatal CHD happened; (5) remain in the state of survival from primary CHD if no event happened; and (6) other nonevent death. CVD risks used in the Markov model were estimated using United Kingdom Prospective Diabetes Study (UKPDS) Risk Engine (version 2)\textsuperscript{8,15} with clinical outcomes measured in the matched-cohort study as the inputs.\textsuperscript{8} Specifically, it was developed based on longitudinal data and took into account factors such as age, sex, race, smoking status, atrial fibrillation, duration of diabetes, levels of Alc, systolic BP (SBP), total cholesterol (TC) and high-density lipoprotein cholesterol (HDL-C) after diagnosis of T2DM.\textsuperscript{15,16}

The inputs for the Risk Engine are discussed in the following sections (Note: the clinical values used as model inputs in the UKPDS Risk Engine are part of the findings of another study by Ip et al.\textsuperscript{8}).

**Model Inputs**

**Clinical inputs for CVD risk prediction.** Clinical inputs used for the estimation of CVD risks were collected from a retrospective matched-cohort study that took place in 2 clinics based out of KP Northern California, a large health maintenance organization (HMO) with an integrated health care model. KP maintains comprehensive medical utilization data that includes an electronic medical record for all patient encounters, laboratory results, and prescriptions using standardized methods.

The sample selection methods for this study are described elsewhere.\textsuperscript{8} Briefly, data for individual patients were collected concurrently from 2 medical facilities for the purpose of
comparison: the enhanced care group (204 patients) and the control group (407 patients). The 2-site design was utilized to address concerns that chronic disease state management studies may be susceptible to contamination, since pharmacists could have been involved in caring for the control group patients.\(^3\) Also, the 2-site design eliminated the potential for a “learning effect” at the same site where physicians may “learn” from the recommendations made by the pharmacist and to pass these recommendations on to patients not being seen by the pharmacist.\(^8\) To further minimize selection bias and ensure patients between the 2 groups were comparable in baseline CVD risks, patients from the 2 groups were matched based on the following characteristics at baseline: age (within 2 years difference), gender, A1c (within 0.8 difference), and Charlson Comorbidity Index (CCI; within 4-point difference). We calculated CCI based on the following baseline characteristics in both groups: CVD with mild or no residual or mini stroke, CVD/stroke/myocardial infarction, dementia, chronic pulmonary disease, ulcer, mild liver disease, hemiplegia, tumor, metastatic solid tumor, leukemia, lymphoma, human immunodeficiency virus but no acquired immunodeficiency syndrome (AIDS), and AIDS. This resulted in 147 matched patients in each group, respectively, in the final analysis.\(^8\) The primary clinical inputs in the Risk Engine, including A1c, SBP, TC, and HDL-C obtained at the end of the 12-month follow-up for both groups, were used to estimate the 10-year CVD risk. As shown in Part A of Table 1, there were no significant differences in the baseline values of the following variables, which were the primary clinical inputs for the UKPDS Risk Engine: A1c (\(P=0.115\)), SBP (\(P=0.184\)), TC (\(P=0.055\)), and HDL-C (\(P=0.475\)).\(^8\) However, patients in the enhanced care group had significant improvements relative to patients in the control group on A1c (\(P<0.001\)), SBP (\(P<0.001\)), and TC (\(P<0.001\)) at the end of the 12-month follow-up. No differences were seen for HDL-C (\(P=0.2835\)).\(^8\)

**Transition probabilities.** Each arrow in Figure 1 indicates a transition from one health state to another, which occurred at yearly intervals. We used the UKPDS Risk Engine to estimate the transition probabilities of various CVD events: absolute risk of fatal and nonfatal CHD and stroke. With the prediction algorithm in this Risk Engine, the observed effects of A1c, SBP, TC, and HDL-C, along with other characteristics at the individual patient level (Part A in Table 1), were translated to the expected 10-year risks for CHD events and stroke (Part B in Table 1). Part B in Table 1 reports the mean risks for the 147 patients in both groups. As shown in Part A Table 1, there was no significant difference between the 2 groups in the 4 major clinical inputs at baseline. Therefore, it is not surprising that there were no significant differences between the 2 groups in the predicted 10-year CVD risk at baseline as a result of matching (\(P=0.18\) for CHD and fatal stroke; \(P=0.176\) for CHD; \(P=0.243\) for stroke).\(^6\) Other transition probabilities include age-dependent noncardiovascular mortality rates, which were derived from the U.S. Vital Statistics.\(^17\) It is also assumed that a nonfatal stroke or CHD event would increase mortality, with the increased risk measured by the relative risk (RR) of death after the event. According to the literature, the RR for death after stroke and CHD is estimated to be 2.318 and 3.719 (Table 2), respectively.

Part B in Table 1 displays the CVD risk estimated by the UKPDS Risk Engine based on the data collected at the 12-month follow-up. These estimates were used as transition probabilities for the 2 hypothetical cohorts of 55-year-old diabetic patients in the Markov model. After 12 months of follow-up, the estimated risks for CHD and stroke (both nonfatal and fatal) were consistently lower in the enhanced care group compared with the control group. The yearly risk increased as the patients aged over the 10-year period in each group. However, it is worth noting that absolute risk reduction (ARR) between the enhanced care group and control group increased over time. For example, the ARR in the nonfatal CHD risk in year 1 was 0.5% (1.2% vs. 0.7%), whereas the ARR increased to 5.5% in year 10 (14.8% vs. 9.3%) in favor of the enhanced care group. Similarly, the ARR between the enhanced control group and care group was calculated as 0.3% for fatal CHD in year 1 and increased to 4.6% in year 10.

**Cost inputs and utilization of medical resources.** We conducted the analysis from the perspective of a third-party payer. Assumptions about the cost of CHD and stroke were derived from the literature as shown in Table 3. We used the Medical Consumer Price Index to generate an inflation factor, which was applied to the past cost figures to convert it to 2011 U.S. dollars. A 3% discount rate was applied to all costs in both branches at base-case analysis.

The total monthly average diabetes-related drug cost per patient was calculated taking into account that patients used different types of medications. Information used in this calculation included the percentage of patients taking 1, 2, or 3 types of medications in each group, the average wholesale price, and the medication adherence rate. For example, the average monthly cost of oral diabetic agents = % of patients on 1 agent \(\times\) price of 30-day supply of metformin + % of patients on 2 agents of metformin and gliptizide \(\times\) price of 30-day supply of the 2 agents + % of patients on the 3 agents of metformin, gliptizide, and pioglitazone \(\times\) price of 30-day supply of the 3 agents. For other medications, including insulin, antihypertensive medications, and antihyperlipidemic medications, the monthly cost per patient was approximated by the percentage of patients on a type of medication multiplied by the corresponding drug costs (Table 3).

Total wage paid to the pharmacist per patient per year was calculated based on the hourly wage rate and the total number...
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### Table 1: Major Clinical Inputs to UKPDS Risk Engine Version 2 and Estimated CVD Risks

#### A. Major Clinical Inputs to UKPDS Risk Engine Version 2

<table>
<thead>
<tr>
<th>Major Clinical Inputs</th>
<th>SBP (mmHg)</th>
<th>Baseline</th>
<th>12-Month Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CG (n=147) Mean</td>
<td>CG (n=147) Mean</td>
<td>ECG (n=147) Mean</td>
</tr>
<tr>
<td></td>
<td>131 (128.6, 133.4)</td>
<td>131 (128.9, 133.1)</td>
<td>128.9 (126.3, 131.6)</td>
</tr>
<tr>
<td></td>
<td>95% CI (9.0, 9.5)</td>
<td>95% CI (9.5)</td>
<td>95% CI (9.2, 9.7)</td>
</tr>
<tr>
<td></td>
<td>189.6 (182.2, 196.9)</td>
<td>189.6 (182.2, 196.9)</td>
<td>179.4 (172.6, 186.2)</td>
</tr>
<tr>
<td></td>
<td>43.4 (41.9, 45.0)</td>
<td>43.4 (41.9, 45.0)</td>
<td>46.6 (42.9, 46.2)</td>
</tr>
</tbody>
</table>

#### B. CVD Risk Estimation Based on the 12-Month Clinical Inputs by UKPDS Risk Engine Version 2

<table>
<thead>
<tr>
<th>Type of CVD Risk</th>
<th>Coronary Heart Disease</th>
<th>Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nonfatal</td>
<td>Fatal</td>
</tr>
<tr>
<td>Forecast Year</td>
<td>Mean (%)</td>
<td>95% CI (%)</td>
</tr>
<tr>
<td>1</td>
<td>CG</td>
<td>1.20 (0.8, 1.8)</td>
</tr>
<tr>
<td></td>
<td>ECG</td>
<td>0.70 (0.5, 1.0)</td>
</tr>
<tr>
<td>2</td>
<td>CG</td>
<td>2.30 (1.7, 3.6)</td>
</tr>
<tr>
<td></td>
<td>ECG</td>
<td>1.50 (1.1, 2.0)</td>
</tr>
<tr>
<td>3</td>
<td>CG</td>
<td>3.80 (2.7, 5.4)</td>
</tr>
<tr>
<td></td>
<td>ECG</td>
<td>2.30 (1.7, 3.1)</td>
</tr>
<tr>
<td>4</td>
<td>CG</td>
<td>5.20 (3.7, 7.4)</td>
</tr>
<tr>
<td></td>
<td>ECG</td>
<td>3.10 (2.3, 4.2)</td>
</tr>
<tr>
<td>5</td>
<td>CG</td>
<td>6.70 (4.7, 9.3)</td>
</tr>
<tr>
<td></td>
<td>ECG</td>
<td>4.00 (3.0, 5.4)</td>
</tr>
<tr>
<td>6</td>
<td>CG</td>
<td>8.20 (5.8, 11.3)</td>
</tr>
<tr>
<td></td>
<td>ECG</td>
<td>5.00 (3.7, 6.6)</td>
</tr>
<tr>
<td>7</td>
<td>CG</td>
<td>9.70 (7.0, 13.4)</td>
</tr>
<tr>
<td></td>
<td>ECG</td>
<td>6.00 (4.5, 8.0)</td>
</tr>
<tr>
<td>8</td>
<td>CG</td>
<td>11.40 (8.1, 15.5)</td>
</tr>
<tr>
<td></td>
<td>ECG</td>
<td>7.00 (5.3, 9.4)</td>
</tr>
<tr>
<td>9</td>
<td>CG</td>
<td>13.10 (9.4, 17.7)</td>
</tr>
<tr>
<td></td>
<td>ECG</td>
<td>8.10 (6.1, 10.8)</td>
</tr>
<tr>
<td>10</td>
<td>CG</td>
<td>14.60 (10.6, 20.0)</td>
</tr>
<tr>
<td></td>
<td>ECG</td>
<td>9.30 (6.9, 12.4)</td>
</tr>
</tbody>
</table>

*P values were obtained from nonparametric Wilcoxon signed-ranks tests.

*UKPDS Risk Engine (version 2) provided the 95% CI for each patient for each type of CVD risk and the means of those risks for the 147 patients in each group were reported.

CG = control group; CI = confidence interval; CVD = cardiovascular disease; ECG = enhanced care group; HbA1c = hemoglobin A1c; HDL-C = high-density lipoprotein cholesterol; SBP = systolic blood pressure; TC = total cholesterol; UKPDS = United Kingdom Prospective Diabetes Study.

of hours spent on initial consultation and follow-up phone calls per month. The average length of consultation was estimated to be 45 minutes for the initial consultation (face to face) and 15 minutes for each follow-up visit (typically via telephone) as recorded from the clinical study. The average number of initial consultation and follow-up visits were identified in the enhanced care group as shown in Table 3. The total physician visit fee per year was calculated by the fee per visit multiplied by the average number of visits per year in each group.

**Utility Measures**

The utility measures for each of the health states in the Markov model were obtained either from the literature or were based on assumptions due to lack of evidence. Utility weight is the degree of preference individuals have for a particular health state or condition. This weight can vary between 0 and 1. By definition, a value of 1 represents perfect health and a value of 0 represents death. A discount rate of 5% was applied to both branches.

All assumptions were subjected to sensitivity analysis (SA). The model assumed that patients have lower utility after the first event of CHD or stroke than patients who remain free of CVD events. In addition, patients will experience a disutility for each additional CHD or stroke after the first event. The utility values used in the study are shown in Table 2.
**TABLE 2** Utility Weights for Health States and Increased Risk of Death Due to CVD Events

<table>
<thead>
<tr>
<th>Utilities for each health states in the Markov model</th>
<th>Base Case</th>
<th>Range for Sensitivity Analysis</th>
<th>Sources</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-ChD</td>
<td>0.77</td>
<td>±30% base</td>
<td>Gage et al.40</td>
</tr>
<tr>
<td>Post-STK*</td>
<td>0.675</td>
<td>(0.6-0.9)</td>
<td>Lampe et al.18</td>
</tr>
<tr>
<td>Additional CHD</td>
<td>-0.055</td>
<td>±30% base</td>
<td>Clarke et al.41</td>
</tr>
<tr>
<td>Additional STK</td>
<td>-0.164</td>
<td>±30% base</td>
<td>Clarke et al.41</td>
</tr>
<tr>
<td>Well</td>
<td>0.782</td>
<td>±30% base</td>
<td>Clarke et al.41</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Relative risk of mortality: increase in risk of mortality relative to all causes mortality

| STK | 2.315 | (1.4-6.4) | Lampe et al.18 |
| CHD | 3.716 | (3.4-7)   | Dennis et al.19 |

*To estimate the stroke utility in the main analysis, it was assumed in the study that 70% of initial strokes were nondisabling, 15% partially disabling, and 15% disabling, based on data from the literature.

CHD = coronary heart disease; CVD = cardiovascular disease; STK = stroke.

**MODEL OUTPUTS**

The key outcomes of interest in the model were incremental cost per quality-adjusted life-year (QALY) gained and life-years gained. The total costs per patient calculated for each arm included costs for medications, treatment costs for nonfatal CVD events, labor costs for pharmacists, and physicians visit fee. Life-years were calculated with different time horizons of the model.

**Major model assumptions.**

1. The base-case scenario of this Markov model assumed that the cohort of simulating patients in both groups achieved the mean values of clinical outcomes (A1C, SBP, TC, and HDL-C) observed at the end of the 12-month follow-up period.

2. For each set of clinical inputs, UKPDS generated a 95% confidence interval (CI) around the estimated mean risks. Mean risks based on clinical inputs at the 12-month follow-up were used in the base-case analysis, while the upper bounds of the 95% CI of risks was evaluated in the worst case scenario and the lower bounds of the 95% CI of the risks in the best case scenario.

3. It was assumed in the base-case analysis that the probabilities of the second and third event would be the same as that of the first-time event predicted by the UKPDS. In recognition of the fact that the UKPDS equation is for a first event only,29 the assumption in the base-case analysis was relaxed in the scenario analysis where the mean odds ratio of the second or third event was 2.33 and ranged from 1.67 to 2.79.

4. To account for the possibility that not all patients will achieve the observed average outcome, we varied the parameter indicating the proportion of patients in the enhanced care group who might not respond to the intervention and revert to their baseline A1C, SBP, and lipid levels. The mean 1- to 10-year risks were then recalculated using the baseline values of those clinical markers instead of the 12-month value as the prediction input. Hence, the transition probabilities of CVD risks for the enhanced
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This study was approved by both Touro University-California Institutional Review Board (IRB Application no. P-0909) and KP Northern California Institutional Review Board (IRB Application no. CN-09Elp-01-H).

Results

Base-Case and Scenario Analyses

Table 4 presents the results of the economic evaluation of the enhanced care group relative to the control group. The model suggests that the enhanced control group dominated the control group with lower treatment cost ($35,740 vs. $44,528) per patient and more life years (8.9 vs. 8.1) and QALY (5.51 vs. 5.02) over the 10-year period. Three types of scenario analysis were conducted. The dominant results of the enhanced care group remained even after evaluating the worst case scenario, when the upper bound of the 95% CI of the risks was used, and the best-case scenario, when the lower bounds of the 95% CI of the risks were applied. In the third scenario, the transition probabilities for the first-time CVD event remained the same as the base case, but the risks for the second and third CVD events were set to 2.33 times higher than the estimated first-time probability by UKPDS.20 Again, the dominant results of the enhanced care group were repeated.

Sensitivity Analysis

Multiple one-way SA. Appendix A shows a selection of the one-way SA (tornado diagram) for the net monetary benefit of using enhanced care. In this diagram, each bar represents the impact of uncertainty in an individual variable on the results. The horizontal bar was generated for each selected variable when the baseline estimate of the variable was varied over plausible ranges (tables 2 and 3), with a wider bar indicating a greater potential effect on the monetary benefit. All parameters were varied around the base-case value within a certain range as specified. The variable identified in the tornado diagram as having the largest impact on the net monetary benefit given a threshold willingness to pay at $50,000/QALY was the time horizon of this analysis, followed by the utility of the health status for diabetic patients free of CVD events (Appendix A). However, all variations in net monetary benefits due to these variables were within the positive range, demonstrating that the enhanced care group remained the preferred strategy. All the remaining variables had nearly no impact on the net monetary benefits.

One-way SA. One-way SA was conducted to examine the individual impact of the adoption of different time horizons on the study outcomes. It is worth noting that as the time horizon was extended for the analysis, the net monetary benefits of the enhanced care group versus the control group increased (see Appendix B). It seems that a minimum of 4 years is needed for the intervention program to achieve higher net monetary

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Strategy</th>
<th>Cost ($)</th>
<th>Life Years</th>
<th>QALY</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base case</td>
<td>ECG</td>
<td>35,740</td>
<td>8.90</td>
<td>5.51</td>
<td>Dominated</td>
</tr>
<tr>
<td></td>
<td>CG</td>
<td>44,528</td>
<td>8.10</td>
<td>5.02</td>
<td>Dominated</td>
</tr>
<tr>
<td>Scenario 1: Low risk</td>
<td>ECG</td>
<td>29,580</td>
<td>9.40</td>
<td>5.783</td>
<td>Dominated</td>
</tr>
<tr>
<td></td>
<td>CG</td>
<td>36,462</td>
<td>8.80</td>
<td>5.413</td>
<td>Dominated</td>
</tr>
<tr>
<td>Scenario 2: High risk</td>
<td>ECG</td>
<td>42,792</td>
<td>8.32</td>
<td>5.166</td>
<td>Dominated</td>
</tr>
<tr>
<td></td>
<td>CG</td>
<td>51,628</td>
<td>7.28</td>
<td>4.568</td>
<td>Dominated</td>
</tr>
<tr>
<td>Scenario 3: 2nd and 3rd event with higher risk</td>
<td>ECG</td>
<td>30,503</td>
<td>8.87</td>
<td>5.420</td>
<td>Dominated</td>
</tr>
<tr>
<td></td>
<td>CG</td>
<td>30,679</td>
<td>7.71</td>
<td>4.810</td>
<td>Dominated</td>
</tr>
</tbody>
</table>

CG = control group; ECG = enhanced care group; QALY = quality-adjusted life-year; T2DM = type 2 diabetes mellitus.
benefits than the control group while holding all other parameters at the base-case scenario. However, this threshold was shortened to 3.3 years when the scenario was changed to the situation that the second and third event had higher odds (OR = 2.33) than the first event.

**Probabilistic sensitivity analysis results.** A cost-effectiveness acceptability curve (Figure 2) showed the likelihood of the intervention being considered cost-effective compared with the control care at various levels of willingness to pay by the payers. Enhanced care was shown to have a consistently higher chance of being the favored strategy regardless of the level of willingness to pay (WTP) if a longer time horizon was adopted: 10 years for base case scenario (Figure 2) and 7 years for the third scenario. In both situations, the shorter the time horizon adopted, the lesser the chance for enhanced care to be preferred. If a 1- to 3-year time horizon was adopted, adding pharmacists into the health care team became less likely to be preferred than using a PCP only in both cases. It seems that at the level of WTP equal to $50,000/QALY, a 5-year time horizon in the base case is the minimum length of time for the program to become the favored strategy given the uncertainty of other factors. However, the minimum length was shortened to 4 years in the third scenario analysis, when second or third events were presumed to occur at a higher rate with OR of 2.33.

Therefore, probabilistic SA results reinforced the importance of correlation between the length of intervention and the magnitude of preventive effects in CVD risk reduction in determining the likelihood of cost-effectiveness of enhanced care.

**Discussion**

Our study, a comprehensive cost-effectiveness analysis of a pharmacist-led diabetes management intervention in a primary care setting, shows that pharmacist intervention can help reduce the long-term CVD risk among patients with T2DM while reducing costs and increasing QALYs. Taking into account the long-term cost savings associated with fewer CVD events, enhanced care (which involves the pharmacist as a member of the primary care team) is a dominant strategy (cost and life saving) compared with the control group (PCP only). The findings of the study were quite robust. The results suggested that it would be cost-effective to incorporate pharmacists into the health care management team for diabetic patients.

It is worth mentioning that previous literature has also documented the effectiveness of a variety of interventions by other health care professionals as well. Diabetes management interventions delivered individually or as a team by physicians, nurses, pharmacists, and other diabetes educators
have been shown to improve patient outcomes in numerous studies.\textsuperscript{24} However, our study differs from previous studies in the intervention strategy, sample populations, and the outcomes and time horizons examined. In order for decision makers to gauge the potential of cost-effectiveness of our pharmacist-led intervention relative to other types of intervention, it is necessary to compare the studies that evaluated other types of intervention with ours. A recent cost-effectiveness analysis study found that nurse specialists gave diabetes care according to a pre-set protocol that was similar to care provided by physicians in terms of quality of life and economic value but with potential savings due to lower labor costs.\textsuperscript{25} In a recent meta-analysis of 11 pre-defined quality improvement (QI) strategies for diabetes, it was shown that the most effective QI strategy was team changes (i.e., the pharmacist or nurse has an active role in patient monitoring and adjusting drug regimens) with further A1c reduction of 0.33% (95% CI 0.28-0.45; 120 trials), LDL cholesterol by 0.10 millimoles per liter (mmol/L; 0.05-0.14; 47 trials), SBP by 3.13 (2.19-4.06; 65 trials), and diastolic blood pressure (DBP) by 1.55 mmHg (0.95-2.15; 61 mmHg trials) versus usual care.\textsuperscript{26} Of particular importance, QI strategies that allowed pharmacists and specialist nurses to make independent changes to drug therapies were found to be most effective. This is exactly the major feature of our pharmacist-led intervention program. Our intervention program has achieved a mean A1c reduction from 9.5% to 6.9% compared with the reduction from 9.3% to 8.4% in the control group after 12 months, resulting in a 1.7% improvement (P<0.001). The patients under enhanced care also experienced a mean reduction of LDL by 10.1 mg/dl, a reduction of SBP by 2.6 mmHg, and a reduction of DBP by 2.3 mmHg. According to the UKPDS, a 1% decrease in A1c is associated with a 37% reduction in microvascular complications and a 21% reduction in the risk of any diabetes-related complication or death.\textsuperscript{19} The degree of A1c reduction due to enhanced care would potentially translate into a 96% decrease in microvascular complications and a 55% reduction in any diabetes-related complication or death.\textsuperscript{26} Using the UKPDS Risk Engine, we found that a 2.6% reduction in A1c among the enhanced care group reduced their 10-year nonfatal CHD risk from 16.4% to 9.3% (a 43% reduction) and the fatal CHD risk from 11.3% to 5.7% (a 50% reduction).\textsuperscript{6} In the findings about costs, available data from the Asheville Project, a longitudinal pre/post cohort study, showed that diabetes patients receiving care from a community pharmacist reduced their mean total direct medical costs by $1,200 while maintaining clinically meaningful improvements in their A1c over a 5-year follow-up period.\textsuperscript{9} The Diabetes Ten City Challenge, a multisite community pharmacy health management program for diabetes patients, also showed a $1,079 in average total health care costs per patient per year.\textsuperscript{10} In our study, we found that the average annual costs over the 10-year period was $3,574 in the enhanced care group versus $4,453 in the control group at base case (Table 4), which translates to $879 savings per year. Another economic study evaluating the cost-effectiveness of strategies for managing people at high risk for diabetes found that the annual diabetes-related cost of an average patient with diabetes was $4,121.\textsuperscript{27} Therefore, the costs incurred by our intervention and cost savings due to the intervention are comparable to other interventions as well. In terms of QALY, the study focusing on life-style intervention among diabetic patients found that the QALY in the 30-year period was calculated as 11.478\textsuperscript{27} with an average of 0.38 QALY per year. Another study conducted in Europe\textsuperscript{28} found that intensive treatment among diabetic patients with 18.6 years of survival had a QALY of 10.2, with an average of 0.5 QALY per year, and it offered a QALY gain of 0.094 per year compared with conventional therapy. In contrast, our study of the 10-year outcome found that the QALY per year averages 0.45-0.57 QALY (Table 4), offering a QALY gain of 0.04-0.07 per year. The higher QALY per year compared with the life-style study might be due to the difference in the cohorts of patients in the 2 studies and the model horizon. The previous study included patients with higher risk for diabetes in the model, and they tended to be older and thus have lower quality of life. However, the lower QALY per year compared with the European study might be because the utility weight assigned to diabetic patients is 0.814 as opposed to 0.782 in our study.

Notably, the SA suggested that 1 of the driving factors of the cost-effectiveness of this program is the time horizon adopted by decision makers. This is partly because the longer-term CVD risk reduction was more dramatic than the short-term reduction as estimated by the UKPDS Risk Engine. Based on our research, if health plans were willing to pay $50,000/QALY, it would take at least 4-5 years for the addition of a clinical pharmacist to the care team to ensure cost-effectiveness to cover all uncertainties factored into the model.

One of the strengths of our study is that the model was primarily based on real-world data, which included clinical effectiveness and health care utilization data collected from 2 comparable clinics with matching baseline data to reduce bias. This is an improvement compared with previous studies that lacked comparison groups and had short follow-up periods (less than 1 year), smaller sample sizes, unequal baseline characteristics across groups, and lack of cardiovascular markers such as BP and lipid levels.\textsuperscript{1} Also, a Markov model was used to simulate 2 matched hypothetical cohorts of patients to estimate the long-term CVD risk reduction.

Another unique contribution of our modeling study was the use of the UKPDS Risk Engine in the projection of cardiovascular outcomes over the long term based on short-term clinical surrogates for T2DM patients. The Risk Engine was
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derived from UKPDS data and was designed to reflect risk in the general T2DM population; therefore, it provided more reliable predictions than the Framingham score adopted by a recent publication.20 The reliability of using the Framingham equation to calculate CHD risk in diabetes patients has been questioned because of the small proportion of diabetes patients in the Framingham study.30 For example, Ladhani et al. (2012) utilized the UKPDS Risk Engine, which is considered a more reliable method of measuring cardiovascular risk in T2DM patients.31 One of the concerns for those adopting the intervention program in the long term might be the difficulty in maintaining the improved outcomes observed at the 1-year follow-up. This concern was addressed in our study by varying the ranges of the key variables—the percentage of patients who would be able to maintain the achieved outcomes from 50% to 100% in the SA. Notably, this variable had minimum impact on the net monetary benefit, suggesting that the approach would still be cost-effective even if a proportion of patients would not be able to maintain the identified improvement as shown in this study.

As the prevalence of diabetes continues to increase and changes in the health care system because of the Patient Protection Affordable Care Act take effect, millions of new patients are expected to need care. The ongoing shortage of primary care practitioners, coupled with the increasing numbers of patients with T2DM, pose significant challenges to the health care system.32 In the face of this shortage, several health care professionals have stepped in to fulfill this role. A recent meta-analysis showed that team-based interventions (i.e., pharmacist or nurse involved in patient monitoring and adjusting drug regimens) was the most effective diabetes management strategy compared with several others.26 In a recent report to the U.S. Surgeon General, pharmacists were singled out as health care professionals who manage disease through medications and other patient care services but are not recognized as health care providers by national health policy in spite of evidence to the contrary.32 Given their expertise and experience, coupled with their accessibility, pharmacists are uniquely positioned to play a much larger role in the health care delivery system.

Currently, the accountable care organization (ACO) concept is being promoted as an integrated approach to managing chronic conditions such as diabetes and is partly driven by the Affordable Care Act.33 Although the act was not explicit about including pharmacists as part of the health care team,33 the U.S. Surgeon General recently recognized that “pharmacy practice models (implemented in collaboration with physicians or as part of a health team) improve patient and health system outcomes and optimize primary care access and delivery.”32 This study provides further evidence of the beneficial clinical and economic potential of including pharmacists in ACOs. In addition, this study also brings attention to the finding that the length of the enrollment period determines the economic benefits of the pharmacists’ preventive efforts. It emphasizes the notion that payers might not be able to reap the benefits of preventive intervention programs targeted at patients with chronic diseases unless they can keep the patients in their plans for a certain period of time.

Limitations

There are limitations to this study worthy of discussion. First, this study relies heavily on evidence generated from a retrospective cohort analysis and was performed at 2 medical facilities using a quasi-experimental study design. A randomized controlled study including a greater number of patients, involving more pharmacist providers and incorporating multiple medical facilities would further enhance the quality of the clinical and economic evidence.

Second, there were different aspects to the pharmacist intervention in this study. However, the quasi-experimental study design did not allow us to estimate the individual effects of those actions on the costs and benefits. Specifically, the improved outcomes in the pharmacist intervention group may have been because of changes in drug dosing, changes of drug regimen, the face-to-face clinical consultation, frequent follow-up phone visits, or improved medication adherence. Those actions were not compared between groups directly; therefore, it is impossible to disentangle the possible multidimensional effects of various intervention strategies. Consequently, it may be difficult for decision makers to decide on the focus of the intervention. Ideally, if it could be established that the frequent pharmacist follow-up phone visits helped improve medication optimization and adherence rates, then the provider might be interested in investing in an intervention program with these features.34,35 If it were the face-to-face contact with pharmacists that was more effective, then the provider might need to make sure adequate physical space (i.e., exam room or private office) is available in the clinical setting. However, the study was not able to identify which management scheme would help contribute most to the improved outcomes. Future studies are necessary to examine the direct impact of specific management strategies on the cost-effectiveness of various pharmacist intervention programs.

A related concern is that the patients in the control group in the retrospective study also experienced various degrees of improvement in outcomes at the end of 12 months.8 Similarly, there is no way to identify the specific causes in the control group responsible for the improvement. If actions taken by pharmacists in the enhanced care group also occurred in the control group, such as monitoring and correction of inappropriate medication use, this could lead to biased estimates of the impact of the intervention. However, this would bias the
results of the study against the intervention group. Another related concern is that our implication for health plans as to the length of intervention required for the same cohort of enrollees in their plans is not clear-cut. Although 4-5 years are identified to be the preferred time horizon, the choice also depends on the magnitude of CVD risk reduction. Four years is found to be the minimum length when second or third CVD events have higher odds to occur, while a longer period of 5 years is needed when assuming all CVD events occur at the probability of a first-time event.

Finally, pharmacist salaries have been a source of concern for providers when considering the implementation of this sort of program. This study suggested that the pharmacist costs have no significant impact on the cost efficiency of implementing the program in the KP HMO setting. There are a few reasons why we should be careful in generalizing the results to other clinical settings. For example, other health care delivery systems might differ from KP in major areas such as facility infrastructure, logistical planning, upfront training costs of pharmacists qualified for managing medication therapy, the nature of the intervention, and the patient population—all of which might influence the cost calculation algorithm. In addition, the KP diabetes population is drawn from an insured population in northern California and may not be representative of other geographic regions, the United States, or other health plans.

Conclusions
In this analysis, we estimated that adding pharmacists to the health care team for the direct management of diabetic patients significantly improved long-term CVD risks. The estimated longer-term CVD risk reduction appears more dramatic than the short-term reduction. The results of the economic model suggest that whether pharmacist intervention provides a cost-effective management tool crucially depends on the length of the effective period of intervention, which is largely determined by the length of time that the patient is enrolled in the health plan. Considering all sources of uncertainty, it seems that a minimum of 4-5 years of consistent enrollment is required for the intervention to be cost-effective without much uncertainty. The study provides insights that will be beneficial for payers to determine whether it is feasible to add pharmacists to the health care team for the direct management of diabetes patients. Future research is needed to improve knowledge about the relative cost-effectiveness of the specific interventions performed by pharmacists in different clinical settings.

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A Markov Model of the Cost-Effectiveness of Pharmacist Care for Diabetes in Prevention of Cardiovascular Diseases: Evidence from Kaiser Permanente Northern California

**APPENDIX A** Tornado Diagram for Multiple One-Way Sensitivity Analysis

Effects on Net Monetary Benefit at Willingness to Pay=$50,000/QALY

- Years of time horizon: 1 to 10
- Utility of health status free of CVD event: 0.6 to 1
- Discount rate of utility: 0.0 to 0.1
- Cost of treatment of CHD ($): 18,731 to 56,193
- Discount rate of cost: 0.01 to 0.05
- Percentage of patients in EG maintaining the improved outcome: 0.5 to 1
- Cost of treatment for stroke ($): 16,458 to 49,374
- Utility of post 1 CHD: 0.7 to 0.84
- Medication compliance rate at baseline: 0.6 to 0.8
- Monthly cost of insulin ($): 50 to 100
- Monthly cost of lipid and pressure medications ($): 25 to 50
- Mean number of types of insulin in pharm’s group: 0.5 to 0.8
- Percentage of increase in adherence in EG: 0.1 to 0.3
- Average hourly wage for pharmacists ($): 40 to 100
- Utility of post-stroke: 0.6 to 0.74
- Utility loss for an additional stroke: 0.0117 to 0.213
- Relative risk of mortality post 1 CHD: 1 to 4.6
- Relative risk of mortality post 1 stroke: 1 to 4.6
- Number of follow-up consultations by pharmacist per year: 8.4 to 10.6
- Utility loss for an additional CHD: 0.0385 to 0.0715
- Relative risk of mortality after more than 2 events: 3 to 7
- Number of initial consultations with pharmacist: 1.1 to 1.3
- Number of visits to physician per year: 2.1 to 2.5
- Physician visit fee: ($) 50 to 200
- Mean number of types of insulin in CG: 0.1 to 0.2
- Percentage of patients in CG maintaining the improved outcome: 0.5 to 1

CG = control group; CHD = coronary heart disease; CVD = cardiovascular disease; EG = enhanced care group; K = thousands.

**APPENDIX B** One-Way Sensitivity Analysis

Net Monetary Benefit (WTP = 50,000)

Number of Years Evaluated in Markov Model

WTP = willingness to pay.
Evaluation of a Novel Web-Based Prior Approval Application for Palivizumab Prophylaxis of Respiratory Syncytial Virus in a State Medicaid Program

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ABSTRACT

BACKGROUND: Recent disproportionate increases in use of specialty medications, such as palivizumab (Synagis), compared with steady utilization of traditional medication use, have prompted complex utilization management strategies that require frequent evaluation to facilitate cost-effectiveness while preserving patient access. Clinical criteria utilized by North Carolina (NC) Medicaid for use of palivizumab for respiratory syncytial virus (RSV) prophylaxis are consistent with the most recent guidelines published in the Red Book: Report of the Committee on Infectious Diseases. Prior to the 2011-2012 RSV season, prior approval (PA) requests were submitted by facsimile using the NC Medicaid Synagis PA form. A web-based PA application, which includes automatic approval capability, monthly dose prompts to providers, and a standardized dose projection formula, was developed for the 2011-2012 RSV season.

OBJECTIVES: To evaluate the timeliness of palivizumab coverage determination, compliance with palivizumab prophylaxis regimen, and the accuracy of the dose projection formula achieved with this novel web-based PA application for palivizumab prophylaxis in NC Medicaid recipients.

METHODS: A historically controlled retrospective cohort study was conducted in which all palivizumab PA submissions and supporting documentation from the 2010-2011 and 2011-2012 RSV seasons were retrospectively reviewed for date and time of original submission and final coverage determination. Submissions from the 2011-2012 season were also retrospectively reviewed for number of doses approved, number of doses administered, date of administration of each dose, and actual dosage administered. These data were used to evaluate compliance and the projected versus actual beneficiary weight and dose to assess the accuracy of the dose projection formula. Submissions lacking required information were excluded. Time from PA submission to coverage determination was compared between seasons using a 2-sample t-test. The proportion of compliant recipients was calculated based on number of doses received and dosing interval of no more than 35 days. Accuracy of the dose projection formula was evaluated using a paired Student’s t-test.

RESULTS: Time to coverage determination decreased overall, on average, by 3.7 days (mean [SD] 8.5 [15.4] vs. 4.8 [9.3]; P < 0.001) for the 2011-2012 season using the electronic web-based PA application compared with the traditional facsimile-based system used in the 2010-2011 season. Decreased time to coverage determination was observed in both PA requests that required medical review and those that did not. Of all palivizumab recipients who were eligible to receive at least 2 doses (n = 1,233), 61.1% were fully compliant with all doses, and 86.9% received all but one documentable dose. Of those who received at least 2 documented doses (n = 1,091), 62.8% received all doses within 35 days of the previous dose. When both definitions of compliance were applied concurrently, 39.3% of all palivizumab recipients were considered compliant; the mean difference between projected and actual doses was 7.1 mg (95% CI: 6.8-7.5; P = 0.001) or 8.6% (95% CI: 8.0-10.0). Projected and actual doses did not vary significantly in the sensitivity analysis when excluding entries with ≥ 50% difference.

CONCLUSIONS: The 2011-2012 web-based PA application improved the timeliness of palivizumab coverage determination compared with the 2010-2011 facsimile-based system. Observed compliance rates for NC Medicaid recipients were slightly lower than those reported in the literature when defined by number of doses received but were higher when defined by interval between doses. The dose projection formula used for the web-based application appears to be accurate for infants 0-2 years of age.


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What is already known about this subject

• National trend reports indicate that the costs for traditional medications remained nearly flat in 2011, while specialty pharmacy expenditures rose approximately 17%.
• Despite evidence of reduced respiratory syncytial virus (RSV)-related hospitalizations, palivizumab has failed to demonstrate consistently positive results in cost-effectiveness studies.
• The American Academy of Pediatrics has published guidelines to target use of palivizumab to infants at highest risk of serious respiratory tract infections associated with RSV.
• Compliance with palivizumab prophylaxis has historically been lower in Medicaid recipients than the commercially insured population.
• Traditional facsimile-based prior approval (PA) systems used for palivizumab may result in significant delay in coverage determination.
• Limited information exists to guide third-party administrators implementing electronic or web-based PA applications.

What this study adds

• This is the first known web-based PA application for palivizumab in the United States with automatic approval capability.
• Features such as automatic approval and ability to upload supporting documentation are effective at decreasing time to coverage determination. The automatic approval feature eliminated a large portion of delay in coverage determination.
Evaluation of a Novel Web-Based Prior Approval Application for Palivizumab
Prophylaxis of Respiratory Syncytial Virus in a State Medicaid Program

What this study adds (continued)

• Palivizumab compliance, prompted with alerts from the web-based application, is slightly higher than rates reported in the literature for Medicaid recipients.
• The dose projection formula used by the web-based application appears to accurately predict the dose amount required regardless of age.

N
atinal trend reports indicate that the expenditures for traditional medications remained nearly flat in 2011, while specialty pharmacy expenditures rose approximately 17%. This is slightly less than the 19.6% increase experienced from 2009 to 2010, but it remains notable due to the consistent annual increases of greater than 15%. Within the realm of specialty medications, the 2011 Drug Trend Report published by Express Scripts cited palivizumab (Synagis) as the seventh most costly specialty medication to state Medicaid programs at close to $4 per member per year.1

Respiratory syncytial virus (RSV) is the leading cause of bronchiolitis in children under 1 year of age and the leading cause of outpatient visits in children under 5 years of age in the United States.2-6 Palivizumab, a humanized monoclonal antibody, was approved by the U.S. Food and Drug Administration (FDA) in 1998 to prevent serious lower respiratory tract disease in infants and toddlers considered to be at high risk for RSV disease. The recommended dose is 15 milligrams per kilogram intramuscularly every 28-30 days, beginning at the start of RSV season.7

Despite demonstrated efficacy,8 conflicting data exist regarding the cost-effectiveness of RSV prophylaxis with palivizumab.9,17 The IMpact-RSV trial (1996-1997), which was used to gain FDA approval for the drug, demonstrated that palivizumab reduced RSV hospitalizations by 55% in high-risk patients who were compliant with the monthly dosing schedule.16 The Palivizumab Outcomes Registry yielded no significant association between compliance and RSV hospitalizations when compliance was defined as the number of expected injections, but when defined as receiving all doses within 35 days of the previous injection, compliance was associated with lower odds of RSV hospitalizations.19 A retrospective claims review of a managed care organization including commercial and Medicaid beneficiaries found compliance—defined as starting palivizumab on time, receiving the expected number of injections, and no more than a 37-day gap between palivizumab claims—was associated with a decreased proportion of patients with at least 1 respiratory-related emergency room (ER) visit. However, compliance so defined was not associated with a decreased proportion of patients with at least 1 respiratory-related office visit or hospitalization. Median total palivizumab and respiratory-related medical costs were similar for compliant and noncompliant patients.17

Medicaid enrollment has been associated with significantly lower compliance rates, as reported in a review of compliance with palivizumab.19 In a claims analysis of Florida Medicaid recipients, 67.9% of Medicaid recipients were considered fully compliant with at least 4 doses of palivizumab, and 41.3% received at least 5 doses, where 5 doses represented ideal coverage.20 Several studies have attempted to identify strategies for increasing compliance through in-home administration programs, telephone calls, and education of caregivers with positive results.15,21-23 In the Palivizumab Outcomes Registry, compliance among Medicaid recipients who received palivizumab in the clinic or office setting was reported as 76% when defined by comparing expected number of doses and actual number of doses received and 61% when compliance was defined as receipt of all palivizumab doses within 35 days of the previous dose. Compliance rates were higher among recipients who were administered palivizumab in the home for both definitions. Data were collected from the medical record and entered into the registry; the number of doses received and 35-day interval between doses were used as definitions of compliance.15

North Carolina Medicaid Palivizumab
Prior Authorization History

While the utilization and total cost of palivizumab to North Carolina (NC) Medicaid has decreased from 2007 to 2011, it remains in the top 25 medications by expenditure, which during the most recent RSV season exceeded $4 per member per year. Also, while the cost per unit and cost per claim have risen across that 4-year period, the total cost per recipient has decreased, leading to a concern that adherence may be an increasing problem.

Clinical criteria utilized by the NC Medicaid prior approval (PA) program for the 2010-2011 and 2011-2012 RSV seasons are consistent with the American Academy of Pediatrics (AAP) and Committee of Infectious Diseases recommendations for use of palivizumab published in the Red Book: 2009 Report of the Committee on Infectious Diseases, 28th edition (Figure 1).24 These guidelines target infants at highest risk of hospitalization and recommend administration only during peak virus circulation, which is November through March in North Carolina. Prior to the 2011-2012 season, NC Medicaid providers submitted PA requests and supporting documentation via facsimile. Requests were approved by pharmacy technicians or pharmacists or escalated to medical review, as necessary. This method required paper-based requests to be scanned and shared electronically among reviewers, which may have resulted in substantial delay in coverage determination. Requests were also frequently submitted lacking information necessary to determine medical necessity, which required
additional attempts to collect missing information. If the provider’s request was approved based on clinical criteria, the appropriate number of doses for the entire season was authorized in response to the request.

Following the 2010-2011 palivizumab season, NC Medicaid received reports from providers that unused vials of palivizumab were accumulating at pediatric practices by the end of the RSV season. While this product wastage was presumed in part to be due to poor compliance, it was also thought that on the day of administration a patient’s dose may have required fewer vials than were dispensed by the pharmacy. Little is known about compliance with Synagis therapy for NC Medicaid recipients in past seasons because claims data are limited for assessing compliance or the time interval between doses. In a published study that compared the consistency of documentation of palivizumab administration in Medicaid claims and medical records from 28 pediatric practices across North Carolina, injection frequencies matched between the 2 data sources for only 46.2% of participants, while dates of administration matched in only 1% of participants.25

In response to identified concerns, NC Medicaid developed a web-based PA application for the 2011-2012 RSV season. Several features of the web-based PA application (developed by Infina Connect, Cary, NC) were designed to address challenges from the 2010-2011 RSV season: (a) the application generated an automatic approval if certain criteria were met based on patient information provided; (b) text box selections, drop-down lists, attachment capability, and free text fields prompted providers to submit requests with all information essential to justify medical necessity; (c) the application required individual dose authorizations to be obtained monthly with provider attestation that the previous dose had been administered; (d) vial quantity for coverage was calculated based on established infant and pediatric growth curves; and (e) dose reminder prompts were sent to providers. It was hoped that the features of the web-based application would decrease product wastage along with other benefits, such as increased transparency of the approval and medical review process to providers, decreased time to coverage determination, and allowed measurement of compliance for all palivizumab recipients.

This study evaluated the effect of the electronic PA request application on timeliness of coverage determination when compared with the prior facsimile-based system, the level of palivizumab injection compliance achieved with the implementation of monthly dose prompts to providers, and the accuracy of the weight and dose projection formula utilized within this system.

Methods

Design

This historically controlled cohort study retrospectively examined all NC Medicaid PA submissions and supporting documentation for palivizumab for the 2010-2011 and 2011-2012 seasons to compare timeliness of palivizumab coverage determination across the 2 seasons. Evaluation of compliance and the dose projection formula were performed using the 2011-2012 cohort only. This study was approved by the University of North Carolina at Chapel Hill Institutional Review Board.

Intervention

The intervention for this study was a novel web-based PA application for palivizumab. The PA application or a medical reviewer may approve up to 5 monthly doses of palivizumab based on clinical criteria (Figure 1). However, in contrast with previous seasons, each monthly dose required individual authorization, which was obtained by attesting to details regarding the administration of the previous dose and providing the patient’s most recent weight. Implementation of required individual dose authorizations aimed to (a) decrease product wastage by collecting information about the patient’s weight to more accurately project the required vial quantity for the next dose and (b) allow for measurement of compliance.
Upon entry of patient information, the application calculated a projected patient weight and corresponding dose 30 days after the date of the last dose. The application then generated an authorization of the appropriate vial size to be dispensed by the pharmacy. The provider faxed this document to the pharmacy as notification of authorization to dispense the next dose. In order to alert providers to potential noncompliance, beginning 40 days after a patient’s last dose request date, providers received weekly prompts via e-mail to request the patient’s next dose.

**Data Sources**

This study used data that were previously collected by NC Medicaid. These data sources included NC Medicaid palivizumab PA request forms, palivizumab PA decision files, and the web-based PA application. AccessCare personnel previously entered the NC Medicaid palivizumab PA data from the 2010-2011 season into a secure electronic database at AccessCare, where the PA files are currently stored. A sample of PA data was checked for reliability of data entry by the primary investigator. Data fields that were selected from the PA data for the 2010-2011 season included date and time of receipt of the PA request form, date and time of final coverage determination, and level of review. The level of review was defined as standard review by a pharmacist and/or technician versus escalation to medical review. In several cases, multiple PA requests were submitted for the same child; only data from the first submission were collected. Additional data collected only from the 2011-2012 season included total number of doses approved, number of doses provider attested to have been administered, date of palivizumab administration, projected patient weight, actual patient weight, and the amount of each dose administered.

**Inclusion and Exclusion Criteria**

Distinct inclusion and exclusion criteria were employed for each major study question.

- **Time to palivizumab coverage determination.** All unique palivizumab PA requests were included in the analysis for the 2011-2012 season. For the 2010-2011 season, requests (16.8%) were excluded because of missing fax and/or coverage decision dates or times or unclear medical review status (Figure 2).

- **Compliance.** All approved palivizumab PA requests for the 2011-2012 season were reviewed for inclusion in the compliance analysis. For analysis of compliance defined by number of doses documented as administered, patients were excluded (21.9%) if they were not eligible to receive at least 2 doses within the season, if no documentation of doses occurred, or if dose amount or date of administration were not documented on a dose request. Patients with multiple requests were also excluded. For analysis of compliance defined by a 35-day administration interval, patients were excluded if documentation of at least 2 doses was not observed (Figure 3).
**FIGURE 4** Sample Selection: Dose Projection Formula Analysis

Dose authorizations for 2011-2012 season (n=5,079)

- No documentation of subsequent dose (n=1,616)
- Dose administration <30 mg or >250 mg (n=570)
- Patient weight >20 kg (n=3)

Individual dose authorizations with subsequent dose documented (n=2,890)

*kg = kilograms, mg = milligrams.*

- **Dose projection formula.** All unique dose authorizations for the 2011-2012 season were reviewed for inclusion in the dose projection formula analysis. Dose authorizations were excluded if information was not available (i.e., last dose of the season; 31.8%), if the documented dose administered was less than 30 milligrams (mg) or greater than 250 mg (11.2%), or if the weight of the infant was documented as greater than 20 kilograms (kg; 0.06%). Exclusion criteria were based upon typical weight and dosing parameters for children ≤2 years of age and maximum dosing limits set by NC Medicaid policy (Figure 4).

**Analysis**

**Time to palivizumab coverage determination.** Time to coverage determination for the 2010-2011 season was calculated as time elapsed from the date and time of the receipt of the PA request to the date and time that coverage determination was entered into the NC Medicaid PA documentation system. For requests received and/or reviewed prior to the start of claims processing for each season, submission and/or the coverage determination date and time were adjusted to the date when claims processing began for the season. An F-test to determine whether the 2 samples had equal variances was conducted using Microsoft Excel (P < 0.001). If the variances were equal, it was assumed that a Student’s t-test could be used to compare means. Given unequal variances between the 2 samples used in this analysis, coverage determination times were compared between the 2 seasons using a 2-sample Student’s t-test assuming unequal variance or a Welch’s t-test to compare means.26

**Palivizumab compliance.** Compliance with palivizumab prophylaxis was defined in 2 ways. The actual number of injections documented as having been received was compared with the expected number to be documented based on the total number of doses approved. Providers were neither required nor incentivized to enter information for the final dose administered. We accounted for this in the expected number of doses to be documented. For example, beneficiaries who received a 5-dose approval in November were expected to have 4 of those doses documented in the web-based application. Patients who received a 2-dose approval in February were expected to have only 1 documented dose in the application. Any patient who received at least as many doses as expected was included in the analysis as being compliant. The second definition of compliance included subjects receiving at least 2 doses and was calculated as the proportion of subjects for whom documentation indicated receipt of all palivizumab doses within 35 days of the previous dose. We reported the proportion of patients who (a) received the total number of approved doses for the season, (b) received all but 1 of the total number of approved doses for the season, (c) received all doses within 35 days of the previous dose, and (d) received all approved doses within 35 days of the previous dose. The 35-day administration interval was selected based on the design of similar compliance analyses.19

**Dose projection formula.** The web-based PA application projected the amount of the next dose based on a standard formula that took into account a recent patient weight and the due date for the next dose. The due date was considered to be 30 days from the date the last dose was administered. Absolute and relative differences between projected and actual doses were calculated and reported using descriptive statistics. Projected and actual dose amounts for individual recipient doses were compared using a paired t-test. A sensitivity analysis, excluding dose differences of greater than 50% to assess for potential bias introduced by system user error, was conducted. Correlation between relative difference and patient age on the date of administration were also assessed using a Pearson correlation coefficient. The projected dose formula is proprietary and therefore is not reported here.

**Results**

**Study Sample and Patient Characteristics**

During the 2010-2011 RSV season, 2,647 unique PA requests were submitted, and 2,366 unique requests were submitted during the 2011-2012 season.

For the 2011-2012 season, all 2,366 unique PA requests were included in the analysis of time to coverage determination: 1,374 were approved by the application, and 992 received medical review. Of the 2,647 unique requests identified for the 2010-2011 season, 414 were excluded because of missing fax and/or coverage decision dates or times, and 30 requests
were excluded because of ambiguity of medical review status; 2,203 requests were included in the analysis (Figure 2). Of the requests included in the analysis, 1,454 were approved by a technician or pharmacist, and 749 received medical review. Demographics of beneficiaries for whom requests were made are shown in Table 1.

For the 2011-2012 season, 1,578 palivizumab PA requests were approved. Of these, patients were excluded for not receiving at least 2 doses within the season (n = 128), when no documentation of doses occurred (n = 178) and when the dose amount or date of administration were not documented on a dose request (n = 34). Five recipients received duplicate case numbers; these were also excluded, leaving 1,233 requests included in the compliance analysis. For analysis of compliance defined by the 35-day administration interval, patients were excluded when documentation of at least 2 doses was not observed (n = 142; Figure 3).

During the 2011-2012 season, 5,079 unique dose authorizations were made. Dose authorizations were excluded when information was not available (i.e., last dose of the season; n = 1,616), when the documented dose administered was less than 30 mg or greater than 250 mg (n = 570), and when the weight of the infant was documented as greater than 20 kg (n = 3). Analysis included 2,890 individual dose authorizations with documented subsequent dose administration (Figure 4).

### Table 1: Beneficiary Characteristics

<table>
<thead>
<tr>
<th>Race</th>
<th>2010-2011 (n = 2,203)</th>
<th>2011-2012 (n = 2,366)</th>
<th>P Value&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>1,165 (53.0)</td>
<td>1,261 (53.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female</td>
<td>1,033 (47.0)</td>
<td>1,105 (46.7)</td>
<td></td>
</tr>
<tr>
<td>Native American/Alaskan</td>
<td>39 (1.8)</td>
<td>39 (1.6)</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>14 (0.6)</td>
<td>29 (1.2)</td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>920 (41.9)</td>
<td>968 (40.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pacific Islander</td>
<td>1 (0.0)</td>
<td>3 (0.1)</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>979 (44.5)</td>
<td>1,127 (47.6)</td>
<td></td>
</tr>
<tr>
<td>Unreported</td>
<td>245 (11.1)</td>
<td>200 (8.5)</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>Based on beneficiaries with prior approval requests for palivizumab.
<sup>b</sup>Represents the level of significance between the 2 seasons, using Pearson chi-square tests for proportions and t-tests for means.
<sup>c</sup>Based on n = 2,198 for the 2010-2011 season due to missing information in the NC Medicaid eligibility database.
<sup>d</sup>Calculated as age at the end of each RSV season to account for beneficiaries born during the season.

### Table 2: Timeliness of Palivizumab Coverage Determination

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>2010-2011 (n = 2,203)</th>
<th>2011-2012 (n = 2,366)</th>
<th>Statistical Difference (P)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean days to coverage determination (SD)</td>
<td>8.5 (15.4)</td>
<td>4.8 (9.3)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Mean days to coverage determination (SD)</td>
<td>3.4 (14.2)</td>
<td>0.0 (0.0)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Mean days to coverage determination (SD)</td>
<td>18.4 (12.7)</td>
<td>11.4 (11.5)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>P value calculated using Student’s t-test assuming unequal variances. SD = standard deviation.

### Time to Palivizumab Coverage Determination

Time to palivizumab coverage determination decreased, on average, by 3.7 days (8.5 to 4.8 days; P < 0.001) for the 2011-2012 season using the web-based PA application when compared with the traditional facsimile-based system used in the 2010-2011 season. Time to coverage determination for cases that did not require medical review decreased from 3.4 days during the 2010-2011 season to zero days in the 2011-2012 season (P < 0.001). Time to coverage determination for cases that required medical review decreased by 7 days, from 18.4 to 11.4 (P < 0.001; Table 2, Figure 5). A multivariate regression analysis was also performed to assess for potential confounding by age of beneficiaries, which showed no significant difference attributed to the difference in age distributions between the 2 seasons.

### Palivizumab Compliance

Of all palivizumab recipients who could have received at least 1 documentable dose (n = 1,233), 61.1% were fully compliant with all documentable doses, and 86.9% received all but 1 documentable dose. Of those who received at least 2 documentable doses (n = 1,091), 62.8% received all doses within 35 days of the previous dose. Of recipients eligible for full season coverage, defined as 4 documentable doses (n = 769), 56.7% were fully compliant with all documentable doses; 81.1% were compliant with at least 3 of 4 documentable doses; and 56.9% received all documentable doses within 35 days of the previous dose. When compliance was defined as receipt of all documentable doses and receipt of all doses within 35-day intervals, 39.3% of all palivizumab recipients were considered compliant compared with 32.6% of recipients eligible for 5 doses (Table 3).

### Dose Projection Formula

Projected doses and actual doses differed, on average, by 7.1 mg or 8.6%. When compared using a paired Student’s t-test, mean
projected and actual doses were significantly different (Table 4). In the sensitivity analysis that excluded projected and actual doses that differed by ≥50%, we observed that some entries for patient weight and dose amount may have been entered erroneously for a given patient but fell within the inclusion criteria based on population values. Projected and actual doses did not vary significantly in the sensitivity analysis (Table 5). Relative difference was not correlated to patient age based on a Pearson correlation coefficient of -0.04.

Discussion

This is the first known web-based PA application that has been utilized in the United States for palivizumab with the capability for automatic approval. Outcomes of this study—including timeliness of coverage determination, compliance, and accuracy of the dose projection formula—were selected based on features designed to improve the PA process. Improving this process is expected to ensure timely receipt of palivizumab for high risk infants and children at the start of and throughout the RSV season as well as reduce wastage of this costly medication.

Time to coverage determination for palivizumab was significantly reduced with implementation of the web-based application. This was due, mostly, to the large number of cases eligible for instant approval based on the diagnosis for the request. Ability to further reduce time to coverage determination was

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**TABLE 3**  Compliance with Palivizumab Regimen Among 2011-2012 Season Recipients

<table>
<thead>
<tr>
<th>Compliance defined by number of doses received</th>
<th>Total Recipients 2011-2012</th>
<th>Recipients Eligible for Full 2011-2012 Seasona</th>
</tr>
</thead>
<tbody>
<tr>
<td>Received all documentable dosesb (n)</td>
<td>n = 1,233</td>
<td>n = 769</td>
</tr>
<tr>
<td>Received all but one documentable doses (n)</td>
<td>61.1% (753)</td>
<td>56.7% (435)</td>
</tr>
<tr>
<td>Compliance defined by interval between doses</td>
<td>n = 1,091</td>
<td>n = 708</td>
</tr>
<tr>
<td>Received all doses within 35 days of previous dose</td>
<td>62.8% (685)</td>
<td>56.9% (403)</td>
</tr>
<tr>
<td>Compliance defined by number of doses received and interval between doses</td>
<td>n = 1,091</td>
<td>n = 769</td>
</tr>
<tr>
<td>Received all documentable doses and received all doses within 35 days of the previous dose</td>
<td>39.3% (429)</td>
<td>32.6% (231)</td>
</tr>
</tbody>
</table>

*aFull season = 5 doses.

bNumber of documentable doses=number of total approved doses minus 1 as providers were not required to document last dose information.

---

**TABLE 4**  Comparison of Projected and Actual Doses for 2011-2012 Season

<table>
<thead>
<tr>
<th></th>
<th>Projected Doses (n = 2,890)</th>
<th>Actual Doses (n = 2,890)</th>
<th>Absolute Difference</th>
<th>Relative Difference (%)</th>
<th>Statistical Difference (P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (mg)</td>
<td>92.4</td>
<td>91.6</td>
<td>0.7</td>
<td>0.8</td>
<td>0.001</td>
</tr>
<tr>
<td>Range (mg)</td>
<td>28.2-221.3</td>
<td>30.0-215.0</td>
<td>0-152.1</td>
<td>0-395.0</td>
<td>-</td>
</tr>
<tr>
<td>95% confidence interval (mg)</td>
<td>-</td>
<td>-</td>
<td>6.8-7.5</td>
<td>8.0-10.0</td>
<td>-</td>
</tr>
</tbody>
</table>

*P value calculated using paired Student’s t-test.

mg = milligrams

---

**TABLE 5**  Comparison of Projected and Actual Doses for 2011-2012 Season: Sensitivity Analysisa

<table>
<thead>
<tr>
<th></th>
<th>Projected Doses (n = 2,830)</th>
<th>Actual Doses (n = 2,830)</th>
<th>Absolute Difference</th>
<th>Relative Difference (%)</th>
<th>Statistical Difference (P)b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (mg)</td>
<td>91.8</td>
<td>91.9</td>
<td>0.3</td>
<td>0.3</td>
<td>0.451</td>
</tr>
<tr>
<td>Range (mg)</td>
<td>28.2-221.3</td>
<td>30.0-215.0</td>
<td>0-75.7</td>
<td>0-99.0</td>
<td>-</td>
</tr>
<tr>
<td>95% confidence interval (mg)</td>
<td>-</td>
<td>-</td>
<td>6.0-6.5</td>
<td>6.7-7.3</td>
<td>-</td>
</tr>
</tbody>
</table>

asensitivity analysis sample excluded all doses with ≥50% difference from projected dose.

bP value calculated using paired Student’s t-test.

mg = milligrams
limited because many providers did not utilize the application’s upload feature to attach documents that would justify medical necessity. Providers instead continued to use facsimile submission for supporting documentation, which required medical reviewer personnel to manually match these documents to requests in the web-based application. Additionally, supporting documentation submitted was often not sufficient to justify medical necessity and frequently required multiple requests to providers for additional information. Further reducing time to coverage determination may streamline the administrative burden of the program and allow infants at high risk of serious respiratory tract infections from RSV to receive palivizumab sooner.

Observed compliance rates in this study were slightly lower when compared with compliance rates reported for Medicaid recipients in the Palivizumab Outcomes Registry, defined as the number of palivizumab doses received compared with expected number of doses (61.1% vs. 76%). When compliance was defined by receipt of all doses within 35 days of the previous dose, we observed a slightly higher rate of compliance in 2011-2012 NC Medicaid recipients than those reported in the Palivizumab Outcomes Registry (62.8% vs. 61%). Monthly injections are recommended during the RSV season based on the 20-day half-life of palivizumab. Thus, compliance with the recommended regimen is needed to maintain serum concentration sufficient to provide prophylaxis throughout the RSV season. Falling serum concentrations as a result of non-compliance can result in hospitalization and wasted expense on previously administered doses. The web-based application evaluated in this study was not initially designed to affect either definition of compliance but rather to provide a means to assess compliance at baseline and have the capability to make system improvements moving forward that may reduce gaps in prophylaxis.

The dose projection formula used within the application appears to be accurate. Given the linear dose projection formula, we suspected that the relative difference in projected and actual doses may vary depending on patient age because pediatric growth curves are not linear between 0 and 2 years of age. However, we did not observe this effect. An accurate dose projection formula is expected to decrease dispensing of excess palivizumab and therefore costs associated with the wastage of the excess medication.

In a recent white paper published by URAC on patient management as a critical component of specialty pharmacy, it was noted that health plans desire compliance and optimal dosage programs more commonly than other therapy management programs. Although this paper was published after the implementation of the web-based palivizumab PA application for NC Medicaid, it is notable that concerns about optimal dosage and adherence were among the top reasons of NC Medicaid to consider a different way of conducting PA.

Implications for Practice
This study has implications for future PA initiatives for palivizumab. While overall timeliness of palivizumab coverage determination decreased significantly because of the instant approval capability of the web-based application, more specific instructions for both the type and submission method of supporting documentation sufficient to justify medical necessity should be included. The compliance rates, based on the interval between doses that were identified through this evaluation, suggest that the window for the e-mail alerts should be shortened. For the upcoming season, the application will e-mail providers beginning at 28 days from the last dose request date. Given the number of entries excluded based on our exclusion criteria for the dose projection algorithm analysis, data verification algorithms could be used in the application to project accuracy of the dose projection formula from erroneously entered values. For instance, dose amounts and patient weights could be compared with population norms and perhaps previous entries for a given patient.

Implications for Research
The findings from this study have implications for future research. Overall, the cost to NC Medicaid for palivizumab claims decreased by just over $3 million from the 2010-2011 season compared with the 2011-2012 season. Interestingly, the average cost per recipient of palivizumab to NC Medicaid was almost identical between the 2 seasons. Future modifications to the application that address accuracy of user entries may decrease wastage, reducing average cost per recipient. The number of recipients with claims for palivizumab decreased by 300 recipients or 20%. The number of requests also decreased by approximately 300, or 11%. The proportion of palivizumab requests approved decreased from 72.8% in the 2010-2011 season to 66.7% in the 2011-2012 season. It is unclear whether the decrease in approved requests and recipients of palivizumab are due to increased inappropriate requests for palivizumab or decreased requests for recipients with legitimate medical necessity. Future research should seek to determine legitimacy of requests and the impact of a web-based application. Additionally, this study was not designed to assess health outcomes related to compliance. These outcomes should be targets for future research.

Limitations
The quality of the 2011-2012 data used for the compliance and dose projection analyses may have been affected by the accuracy of data entry by application users. We attempted to control for potentially erroneously entered values in our exclusion criteria; however, values may have been included in the sample that would have appeared appropriate for the population but inappropriate for a particular patient. In order to correct for bias introduced by this error, we conducted a
sensitivity analysis for the dose projection formula evaluation. We were unable to assess for bias because of differences in the distribution of the population by diagnosis for each season due to poor image quality of requests submitted by facsimile. We included a multivariate analysis to account for bias because of distribution of age of beneficiaries receiving palivizumab for both seasons. Additionally, we relied on a date and time stamp on each PA request from the receiving fax machine as the date received. These machines may not have been calibrated accurately, introducing systematic error. Several PA requests in both the 2010-2011 and 2011-2012 seasons were submitted prior to the start of the RSV season. Because reviewers did not necessarily review early requests when received, we used the date that claims processing could begin for palivizumab as the date received and/or date decision for any preceding the date claims processing began. We did not include the final dose of palivizumab for any beneficiaries in the analyses because providers were neither required nor incentivized to enter information about the last dose of palivizumab administered, and palivizumab claims data has limitations discussed elsewhere. This potential limitation was addressed by consistently omitting the last dose for each beneficiary in our compliance calculations.

### Conclusions

The 2011-2012 web-based PA application was associated with improved timeliness of palivizumab coverage determination when compared with the 2010-2011 facsimile-based system. Observed compliance rates for NC Medicaid recipients were slightly lower than those reported in the literature when defined by the number of doses received but were higher when defined by the interval between doses. The dose projection formula used for the web-based application appears to be accurate for infants 0-2 years of age.

### DISCLOSURES

There was no external funding for this study, and the authors report no conflict of interest associated with this study. Concept and design were performed by all authors. Data were collected by Lundeen. Data were interpreted by Lundeen, O’Brien, Pfeiffenberger, and Jacobson Vann. Writing of the manuscript was performed by Lundeen, Pfeiffenberger, and Jacobson Vann. The manuscript was revised by all authors. The authors wish to acknowledge Greg Moyer, Matthew Caldwell, and Hannah Wigmore for assistance with data collection and Troy Trygstad, PharmD, PhD, for his assistance with manuscript review.

### REFERENCES


Evaluation of a Novel Web-Based Prior Approval Application for Palivizumab
Prophylaxis of Respiratory Syncytial Virus in a State Medicaid Program

Adherence to Varenicline and Associated Smoking Cessation in a Community-Based Patient Setting

Joshua N. Liberman, PhD; Marc J. Lichtenfeld, PhD; Aaron Galaznik, MD; Vera Mastey, BPharm, MS; James Harnett, PharmD, MPH; Kelly H. Zou, PhD; Joseph B. Leader, BA; and H. Lester Kirchner, PhD

ABSTRACT

BACKGROUND: Varenicline, a selective α4β2 nicotinic acetylcholine receptor partial agonist, is a pharmacotherapy indicated for smoking cessation treatment. To our knowledge, no studies have described varenicline treatment adherence and efficacy from real-world treatment patterns in a U.S. primary care setting.

OBJECTIVE: To estimate adherence to varenicline prescription orders and subsequent quit rates among smokers in a primary care setting.

METHODS: In this retrospective cohort study, eligible patients were enrolled with Geisinger Health Plan, had an initial varenicline prescription written by a Geisinger provider between January 1, 2006, and December 31, 2009, and had a follow-up clinic visit within the subsequent 12 months. Adherence was derived from linking electronic prescriptions with adjudicated pharmacy claims. Smoking status was collected at each health care encounter.

RESULTS: Of the 1,477 eligible patients, 823 (55.7%) were primary nonadherent, having failed to initiate on the prescribed varenicline therapy. Of the remaining 654 patients, 359 (54.9%) were adherent, having completed a full 12-week course of therapy, and 295 (45.1%) were partially adherent, having initiated but not completed the full course of therapy. A total of 521 patients (35.3%) ceased smoking during the 12-month follow-up period: 182 (50.7%) of the adherent cohort, 82 (27.8%) of the partially adherent population, and 257 (31.2%) of the nonadherent cohort. No significant difference was found in quit rates between the partially adherent and nonadherent patient cohorts (adjusted HR 0.88 [95% CI = 0.69-1.13]). However, patients adherent to the varenicline regimen were almost twice as likely to succeed in quitting smoking compared with completely nonadherent patients (HR 1.93 [95% CI = 1.59-2.33]).

CONCLUSION: Smoking cessation occurred more often among individuals adherent to varenicline therapy; however, medication nonadherence was common. After prescribing varenicline, clinicians and payers could consider active patient follow-up to maximize adherence and optimize treatment outcomes.

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What this study adds

• Varenicline is an effective smoking cessation therapy that increases the odds of quitting smoking compared with placebo. Two large randomized, double-blind, placebo-controlled trials (Gonzales et al. 2006; Jorenby et al. 2006), each randomizing over 1,000 healthy adult smokers to treatment with varenicline, sustained-release (SR) bupropion, or placebo, reported abstinence rates after the 12-week treatment period of 44.0% for the varenicline groups. The benefit of varenicline has been confirmed in a Cochrane meta-analysis, which estimated that use of varenicline was associated with a two- to three-fold increase in the odds of quitting compared with pharmacologically unassisted attempts.
• Owing to differences in populations and available levels of support to quit smoking, the results of randomized controlled trials in smoking cessation do not necessarily translate to those achieved in the real-world setting. Although the reported abstinence rates from observational studies have been encouraging, the results fall over a large range, and some studies report an underestimation of smoking status in groups such as pregnant women and those with respiratory disease.
• There is a gap in the literature on level of adherence to smoking cessation therapy and the impact that this has on abstinence rates. To our knowledge, there are no previously published studies of adherence to smoking cessation pharmacotherapy in a real-world setting, and there is limited information information in clinical and observational trials.

What is already known about this subject

• Approximately 20% of Americans are addicted to smoking, and this addiction is responsible for nearly 445,000 deaths annually. Although 70% of smokers report that they want to quit, less than half attempt to quit, and only 4%-7% are successful.
The recording of smoking status was collected during the patient assessment and medication reconciliation process and was reported at all subsequent visits during the 12-month follow-up period.

Geisinger Clinic is a multispecialty practice that has 57 sites and 730 employed physicians and physician’s assistants. The patient population includes residents from central and northeastern Pennsylvania. Between 1996 and 2001, the Epic Systems Corporation EHR system was installed in all clinic community practice sites, medical centers, and specialty clinics. Although patients in the system have insurance coverage through a range of payers, all subjects in this study were members of the Geisinger Health Plan, which covers approximately 30% of patients seeing physicians in the system. Smoking status is assessed at all office visits as part of routine data gathering as per standard Geisinger Health System procedures and logged in the EHR. The study protocol was approved by the Geisinger Institutional Review Board.

To be eligible for inclusion, an individual must have had a prescription recorded in the EHR for an initial order for varenicline between January 1, 2006, and December 31, 2009, and at least 1 follow-up clinic visit within the subsequent 12-month period. Initial and continuing prescriptions were identified by the medication name or dose. Initial prescriptions were either named “CHANTIX STARTING MONTH PAK” or were written as 0.5 milligram (mg) tablet. Continuing prescriptions were either named “CHANTIX CONT MONTH PAK” or were written as a 1 mg tablet. Initial prescriptions were used to ensure that the patient was beginning a new course of varenicline. As of the index prescription order date, the participant must have been aged 18 years or older, enrolled with a Geisinger primary care physician, and had pharmacy insurance benefits provided through Geisinger Health Plan prior to the initial prescription order. The majority of subjects in the study had equivalent benefit coverage and out-of-pocket costs for smoking cessation treatments, including Chantix.

**Variables and Definitions**

Data were extracted from both the EHR and paid pharmacy claims files. The following variables were selected from the EHR: demographics; encounter data (e.g., office visits); comorbidities; prescription dates; smoking status; and date of smoking cessation, if achieved. Smoking cessation success or failure was defined in this study based on subject response to querying about smoking status during office visits subsequent to, but within 12 months, of index date, as recorded in the EHR. Comorbidities were defined by an *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) code associated with 2 outpatient visits or listed on the problem list; comorbidities were compiled into the Charlson Comorbidity Index.\(^7\) All paid claims for smoking cessation medications,
including dates of purchase, days' supply, and National Drug Code (NDC) number, were extracted from insurance pharmacy claims files.

A full course of varenicline therapy is routinely considered to comprise 1 full week of therapy before, and 12 weeks of therapy following, the initial smoking abstinence date. If smoking abstinence is maintained, an additional 12 weeks of treatment is recommended to increase the likelihood of sustained abstinence.6 Adherence metrics were derived through linking prescription order records to matching claims. Linking the medication prescriptions from the EHR to the pharmacy claims was performed by identifying all prescriptions in the EHR for varenicline and then looking for a pharmacy claim on or after the date of the prescription with an NDC for varenicline. Applying the definition of a full course of varenicline therapy described above, each participant was categorized as adherent, partially adherent, or nonadherent. Adherent individuals were those who purchased at least a 90-day supply during the

113 days following the index prescription fill. This definition required patients to complete the 3-month course of therapy with available drug on at least 80% of days. Individuals with drug available >0% to <80% of days were deemed partially adherent. Participants with no paid pharmacy claim for varenicline in the 12-month period following the prescription order were deemed nonadherent.

**Statistical Analysis**

Comparisons between adherence groups were conducted using the nonparametric Kruskal-Wallis test for continuous data and the Pearson chi-square test for categorical data. The association between adherence and smoking cessation was assessed using nonparametric Kaplan-Meier curves, which displayed the monthly cumulative incidence of smoking cessation following the varenicline order. Patients who did not achieve sustained smoking cessation by 12 months, including those who reported quitting in 1 visit and then reported smoking in a subsequent visit, were not considered censored for Kaplan-Meier curves until 1 year. Smoking cessation rates among the different adherence groups were compared using the log-rank test and Cox proportional hazards model controlling for potential confounding variables. Variables that differed significantly across adherence groups (P<0.10) were considered in the regression model. Model results are presented as hazard ratios (HRs) and 95% confidence intervals (CIs).

All analyses were performed using the Statistical Analysis System (SAS) version 9.2 (SAS Institute Inc., Cary, NC). Two-sided P values were reported, and a P value of <0.05 was considered statistically significant.

**Results**

Subject disposition is shown in Figure 1. A total of 13,303 patients received a varenicline prescription during the enrollment period. Of these, 4,092 (30.8%) had eligible pharmacy insurance coverage, and 3,709 (27.9%) were starting pack orders, indicating that their prescriptions were intended to initiate therapy. A total of 1,477 (11.1%) individuals had at least 1 visit with an eligible provider during the 12-month follow-up period (and thus had smoking status re-assessed); 2,232 had no follow-up visit and were excluded.

The eligible study sample (n=1,477) was predominantly female (58.2%), Caucasian (98.4%), married (62.3%), had a mean age of 49.1 years, was overweight—with a median body mass index (BMI) of 28.3—and had average systolic and diastolic blood pressure readings of 124.1 and 74.7 mmHg, respectively (Table 1). The most common comorbid conditions were diabetes (13.9%), chronic obstructive pulmonary disease (9.4%), cardiovascular disease (8.6%), coronary artery disease (8.5%), and asthma (8.0%). The median number of packs of cigarettes smoked per day at baseline was 1.
TABLE 1  
Geisinger Health Plan Patients with Varenicline Order (N = 3,709) by 12-Month Follow-Up Status

<table>
<thead>
<tr>
<th>Variable</th>
<th>No Visit Within 12 Months of Order (n = 2,232)</th>
<th>Study Sample (n = 1,477)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male (%)</td>
<td>49.6</td>
<td>41.8b</td>
</tr>
<tr>
<td>Age at baseline (mean)</td>
<td>44.2</td>
<td>49.1b</td>
</tr>
<tr>
<td>Caucasian (%)</td>
<td>97.8</td>
<td>98.4</td>
</tr>
<tr>
<td>Married (%)</td>
<td>59.4</td>
<td>62.3</td>
</tr>
<tr>
<td>Body mass index (median)</td>
<td>27.1</td>
<td>28.3b</td>
</tr>
<tr>
<td>Systolic blood pressure (mean)</td>
<td>121.0</td>
<td>124.1b</td>
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<tr>
<td>Diastolic blood pressure (mean)</td>
<td>73.9</td>
<td>74.7b</td>
</tr>
<tr>
<td>Flu vaccination (% baseline)</td>
<td>22.8</td>
<td>35.8b</td>
</tr>
<tr>
<td>Pneumonia vaccination (% baseline)</td>
<td>9.3</td>
<td>16.6b</td>
</tr>
<tr>
<td>Cigarettes, packs/day at baseline (median)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Previous bupropion use (%)</td>
<td>4.2</td>
<td>7.6b</td>
</tr>
<tr>
<td>Previous NRT use (%)</td>
<td>1.0</td>
<td>2.1c</td>
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<tr>
<td>Comorbidities (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>COPD</td>
<td>6.0</td>
<td>9.4b</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>3.8</td>
<td>8.5b</td>
</tr>
<tr>
<td>Asthma</td>
<td>7.3</td>
<td>8.0</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>1.3</td>
<td>3.7b</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>4.2</td>
<td>8.6b</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>4.8</td>
<td>13.9b</td>
</tr>
<tr>
<td>Cancer, any</td>
<td>4.5</td>
<td>5.8</td>
</tr>
<tr>
<td>Cancer, lung</td>
<td>0.4</td>
<td>0.5</td>
</tr>
<tr>
<td>Charlson Comorbidity Index (%)</td>
<td></td>
<td></td>
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<tr>
<td>0</td>
<td>76.0</td>
<td>60.9</td>
</tr>
<tr>
<td>1-3</td>
<td>23.3</td>
<td>36.0</td>
</tr>
<tr>
<td>4+</td>
<td>0.7</td>
<td>3.0</td>
</tr>
</tbody>
</table>

^aP<0.05  
bP<0.001  
cP<0.01
COPD = chronic obstructive pulmonary disease; NRT = nicotine replacement therapy.

TABLE 2  
Distribution of Select Characteristics Among the 1,477 Study Participants by Adherence^a to Varenicline Therapy

<table>
<thead>
<tr>
<th>Variable</th>
<th>Entire Sample (n = 1,477)</th>
<th>Primary Non-adherent (n = 823)</th>
<th>Partially Adherent (n = 295)</th>
<th>Adherent (n = 359)</th>
<th>P Value^b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male (%)</td>
<td>41.8</td>
<td>41.8</td>
<td>40.7</td>
<td>42.9</td>
<td>NS</td>
</tr>
<tr>
<td>Age (years, mean)</td>
<td>49.1</td>
<td>49.9</td>
<td>47.7</td>
<td>48.5</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Caucasian (%)</td>
<td>98.4</td>
<td>98.4</td>
<td>98.6</td>
<td>98.0</td>
<td>NS</td>
</tr>
<tr>
<td>Married (%)</td>
<td>62.3</td>
<td>62.8</td>
<td>54.6</td>
<td>67.4</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Body mass index (median)</td>
<td>28.3</td>
<td>28.2</td>
<td>28.3</td>
<td>29.0</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg, mean)</td>
<td>124.1</td>
<td>124.2</td>
<td>122.6</td>
<td>125.2</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg, mean)</td>
<td>74.7</td>
<td>74.5</td>
<td>74.5</td>
<td>75.2</td>
<td>NS</td>
</tr>
<tr>
<td>Influenza vaccination (%)</td>
<td>35.8</td>
<td>36.2</td>
<td>35.6</td>
<td>35.1</td>
<td>NS</td>
</tr>
<tr>
<td>Pneumonia vaccination (%)</td>
<td>16.6</td>
<td>16.5</td>
<td>17.6</td>
<td>15.9</td>
<td>NS</td>
</tr>
<tr>
<td>Previous bupropion use (%)</td>
<td>7.6</td>
<td>0.5</td>
<td>15.6</td>
<td>17.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Previous NRT use (%)</td>
<td>2.1</td>
<td>0.0</td>
<td>6.4</td>
<td>3.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Comorbidities (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>COPD</td>
<td>9.4</td>
<td>9.2</td>
<td>10.8</td>
<td>8.6</td>
<td>NS</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>8.5</td>
<td>9.5</td>
<td>6.1</td>
<td>8.1</td>
<td>NS</td>
</tr>
<tr>
<td>Asthma</td>
<td>8.0</td>
<td>7.4</td>
<td>8.1</td>
<td>9.2</td>
<td>NS</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>3.7</td>
<td>3.8</td>
<td>3.4</td>
<td>3.6</td>
<td>NS</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>8.6</td>
<td>9.4</td>
<td>7.1</td>
<td>8.1</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>13.9</td>
<td>13.8</td>
<td>13.2</td>
<td>14.5</td>
<td>NS</td>
</tr>
<tr>
<td>Cancer, any</td>
<td>5.8</td>
<td>5.5</td>
<td>5.8</td>
<td>6.7</td>
<td>NS</td>
</tr>
<tr>
<td>Cancer, lung</td>
<td>0.5</td>
<td>0.2</td>
<td>1.4</td>
<td>0.3</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Charlson Comorbidity Index (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>60.9</td>
<td>60.9</td>
<td>61.0</td>
<td>61.0</td>
<td>NS</td>
</tr>
<tr>
<td>1-3</td>
<td>36.0</td>
<td>35.4</td>
<td>37.3</td>
<td>36.5</td>
<td></td>
</tr>
<tr>
<td>4+</td>
<td>3.0</td>
<td>3.8</td>
<td>1.7</td>
<td>2.5</td>
<td>NS</td>
</tr>
<tr>
<td>Office visits, past 6 months (median)</td>
<td>2.0</td>
<td>2.0</td>
<td>2.0</td>
<td>2.0</td>
<td>NS</td>
</tr>
</tbody>
</table>

^aNonadherence, adherence, and partial adherence were defined as having no pharmacy claims, at least a 90-day supply, and a 1- to 89-day supply of varenicline, respectively, during the 113-day follow-up period.  
bP<0.05  
cP<0.01
COPD=chronic obstructive pulmonary disease; mmHg=millimeters of mercury; NRT=nicotine replacement therapy; NS=not significant.

Compared with the 2,232 ineligible patients (who met all eligibility criteria except the requirement to have at least 1 clinic visit during the 12-month follow-up period), eligible patients were significantly more likely to be female (50.4% vs. 58.2%, respectively; P<0.001), older (44.2 vs. 49.1 years, respectively; P<0.001), and to have a higher BMI, higher systolic and diastolic blood pressure, and higher rates of comorbid health conditions. The 2 samples had comparable smoking histories. Eligible patients had higher rates of prior bupropion and NRT use (Table 1).

A total of 823 (55.7%) eligible patients were primary nonadherent, having failed to initiate prescribed varenicline therapy. Of the remaining 654 patients, 359 (54.9%) were adherent, having completed a full course of therapy, and 295 (45.1%) were partially adherent, having initiated but not completed the full course of therapy. The adherent, partially adherent, and nonadherent cohorts were similar on most baseline characteristics, with borderline significant differences in age, marital status, systolic blood pressure, and history of lung cancer (Table 2). Compared with nonadherent patients, the adherent cohort was significantly more likely to have a history of bupropion (0.5% vs. 17.6%, respectively; P<0.001) and NRT (0% vs. 3.3%, respectively; P<0.001) use.
Adherence to Varenicline and Associated Smoking Cessation in a Community-Based Patient Setting

Overall, 521 (35.3%) participants ceased smoking during the 12-month follow-up period. Among the primary nonadherent cohort, nearly 31% reported quitting, a rate that was similar to that of the partially adherent cohort (28%). Among the fully adherent cohort, 50.7% reported cessation (P<0.001; Figure 2). The smoking cessation curves for the partially adherent and primary nonadherent cohorts were not significantly different (P=0.29), and each was different from the adherent cohort (both with P values of <0.001).

After adjustment for age, marital status, systolic blood pressure, and presence of lung cancer, the HR using the proportional hazards regression model for quitting was 1.93 (95% CI=1.59-2.33; P<0.0001) and 0.88 (95% CI=0.69-1.13; P=0.3253) for the adherent and partially adherent cohorts, respectively, compared with the primary nonadherent cohort (Table 3).

Discussion

Among the 1,477 eligible patients prescribed varenicline, only 24% were adherent to the recommended 3-month course of therapy. Fifty-six percent of patients did not initiate therapy, and 20% initiated therapy but discontinued before completing the recommended course. Twelve-month smoking cessation rates were similar between the nonadherent (31.2%) and partially adherent (27.8%) cohorts. The smoking cessation rate among the fully adherent cohort reached 50.7%.

To our knowledge, there are no published studies of primary nonadherence to smoking cessation pharmacotherapy. However, in a survey of 1,219 adults who reported recent use of smoking cessation medications, Balmford et al. (2011) reported that only 40% of individuals remained adherent for more than 8 weeks and that nonadherence was associated with medication side effects, lack of efficacy, and patient perception of the need for medication.

The abstinence rate among the 359 individuals who completed therapy is comparable with that reported in clinical trials. In a randomized, double-blind, placebo-controlled trial of 1,025 healthy adult smokers who were randomized to treatment with varenicline, bupropion SR, or placebo, Gonzales et al. (2006) reported an abstinence rate in those receiving varenicline of 44.0% after the 12-week treatment period, which decreased to 21.9% at 52 weeks. In a similarly designed trial, Jorenby et al. (2006) reported abstinence rates in varenicline users of 43.9% and 23% at weeks 12 and 52, respectively. Since our results pertain to individuals who sustained smoking abstinence during the 12-month follow-up period, our estimate of 50.7% indicates a comparable effectiveness rate among those who completed therapy in the community setting.

This study highlights the importance of initiating and completing the recommended treatment course of varenicline, subsequent to being motivated to succeed in a quit attempt. Individuals who completed the full course of therapy were 93% more likely to quit smoking than those who did not. This result is comparable with estimates reported in a recent meta-analysis of placebo-controlled smoking cessation trials, in which the odds of successful smoking cessation associated with varenicline use were 2.4 (95% CI=1.9-3.1).11

This study has numerous strengths. The study sample was large and involved over 1,000 primary care patients with experience of varenicline treatment. The limited exclusion criteria resulted in a study sample that was representative of a typical primary care population, with high comorbidity burdens and a diverse range of prior treatment histories, as opposed to the
homogeneous and otherwise healthy populations enrolled in randomized trials. Finally, at Geisinger Clinic, smoking status is considered an essential measure, equivalent to height, weight, blood pressure, and pulse rate, and is recorded by trained nurses at every clinical visit, thereby minimizing the potential for recall bias.

**Limitations**

Because the present investigation was an observational study, outcomes were subject to selection bias, and associations between treatment and outcomes cannot be deemed causal. Though we detected few differences in measured characteristics between adherent and nonadherent cohorts, there is likely an association between adherence and unmeasured confounders, most notably participation in counseling or other behavioral interventions, and also with the patient’s general desire and readiness to quit smoking. As the data set comprised EHR and pharmacy claims data, but not medical claims, participation in these programs was not verifiable. Access to behavioral interventions provided by Geisinger, however, did not differ across the cohorts in this study. Polypharmacy for smoking cessation was also not examined as part of this study, as concomitant bupropion use levels were low (data not shown) and use of NRT purchased over the counter was not obtainable through pharmacy claims. There is also a known association between number of quit attempts and likelihood of quit success.\(^{12}\) While higher associations of prior bupropion and NRT use were seen in the adherent group, there were insufficient longitudinal data to examine the role of number of prior quit attempts in this study. Further, smoking status was self-reported by patients. Undesirable behaviors, such as smoking, may be under-reported by patients; however, when collected by interview (in this case, by roaming nurses) they tend to have high sensitivity and specificity.\(^{13}\) Additionally, the demographics of Geisinger’s primary care population may limit the generalizability of findings to other populations.

**Conclusion**

Primary medication nonadherence was high in this patient sample and was attributable primarily to patients electing not to initiate prescribed therapy. The HR for quitting smoking for individuals who adhered to varenicline therapy was 1.93 compared with those who failed to initiate therapy. Taking these findings into consideration, future research should focus on causal factors and on the development and implementation of early interventions to support medication adherence, particularly those interventions that monitor adherence and smoking cessation outcomes in near real time.

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**DISCLOSURES**

This study was sponsored by Pfizer Inc, the manufacturer of varenicline. Four authors are employees of Geisinger Health System who were paid consultants to Pfizer in connection with the development of this manuscript. Four authors are employees of Pfizer Inc. Scientific writing support was provided by Ilene Ladd from Geisinger Health System and was funded by Pfizer Inc. Editorial support was provided by Helen Jones at UBC Scientific Solutions and was funded by Pfizer Inc.

Galaznik, Mastej, Harnett, and Zhou contributed to the study design, Lichtenfeld, Leader, and Kirchner contributed to data collection; Kirchner, Zhou, Liberman, and Galaznik contributed to data interpretation. Liberman, Galaznik, Zhou, and Leader wrote the manuscript, while Liberman, Mastej, Harnett, Galaznik, Zhou, and Kirchner revised the manuscript.

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**REFERENCES**


Adherence to Varenicline and Associated Smoking Cessation in a Community-Based Patient Setting


Guideline-Recommended Medications: Variation Across Medicare Advantage Plans and Associated Mortality

Alfredo J. Selim, MD, MPH; Benjamin G. Fincke, MD; William H. Rogers, PhD; Shirley Qian, MS; Bernardo J. Selim, MD; and Lewis E. Kazis, ScD

ABSTRACT

OBJECTIVES: To evaluate variation in the prescription of guideline-recommended medications across Medicare Advantage (MA) plans and to determine whether such variation is associated with increased mortality.

METHODS: Observational study of 111,667 patients aged 65 years or older receiving care in 203 MA plans. We linked data from the Medicare Health Outcomes (HOS) Survey cohort 9 (April 2006–May 2008) with the Medicare Part D prescription benefit files (January 1, 2006–December 31, 2007) to examine variation in treatment across MA plans and its association with differences in observed (O)/expected (E) mortality ratio for 5 high-volume chronic conditions: diabetes, coronary artery disease (CAD), congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD)/asthma, and depression.

RESULTS: Analysis of variance confirmed that the 203 MA plans differed significantly in their use of guideline-recommended treatment ($P \leq 0.02$). Those MA plans with higher use of angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers ($r = -0.40; P < 0.0001$) and beta-blockers ($r = -0.27; P < 0.0001$) in patients with CHF were significantly associated with lower O/E mortality ratios. Those MA plans with higher use of multiple guideline-recommended medications were significantly associated with lower O/E mortality ratios in CHF ($r = -0.45; P < 0.0001$) and diabetes ($r = -0.14; P < 0.042$). There were no significant associations between the variation in performance indicators and mortality ratios in patients with CAD and COPD/asthma. Those MA plans with higher use of antihypertensive medications had significantly higher O/E mortality ratios ($r = 0.28; P < 0.0001$).

CONCLUSIONS: There was wide variation across MA plans in the prescription of guideline-recommended medications that had a measurable relationship to the mortality of elderly patients with CHF and diabetes. These findings can serve to both motivate and target quality improvement programs.


What this study adds

- Variation of guideline-recommended medications has a measurable effect on patient outcomes.

Medicare Advantage (MA) plans provide care to 23% of the nearly 45 million Medicare-eligible patients. As a result of their age, Medicare patients are likely to be a fragile group with higher mortality when not treated according to clinical practice guidelines. Therefore, it is expected that variations in the achievement of life-prolonging outpatient treatment at the plan level would affect survival. In a previous study, the 2-year mortality rate of patients receiving care in MA plans was 7.3%. We did find significant variation in mortality rates across MA plans, ranging from 3.4% to 14.6% (results not published).

Elderly patients tend to receive fewer evidence-based therapeutic interventions than younger, lower-risk patients. Those with heart failure, for example, are less likely to receive evidence-based treatments. They are prescribed angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, and anticoagulants less frequently than younger patients. Likewise, few patients with diabetes are taking aspirin (44%), lipid-lowering (20%), or ACE inhibitor (39%) therapy. Though failure to prescribe medications such as these can affect patient survival, we have been unable to find any studies that examine the degree to which variation in prescribing across clinics or health care systems is associated with measurable survival differences.

The specific objectives of this study were (1) to evaluate the variation across MA plans of guideline-recommended use of medications for 5 high-volume diagnoses—diabetes, coronary artery disease (CAD), congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD)/asthma, and depression—and (2) to examine whether variation in guideline-recommended medications across MA plans is associated with differences in risk-adjusted mortality.

Methods

Study Population

The study population consisted of respondents to the Medicare Health Outcomes Survey (HOS), which is a national survey...
to measure the quality of life and functional health status of Medicare beneficiaries enrolled in managed care. The Medicare HOS dataset includes information about enrollees’ demographics, socioeconomics, health status and disability, medical history, and date of death.

We used the Medicare HOS cohort 9 (April 2006–May 2008) because on January 1, 2006, the Centers for Medicare and Medicaid Services (CMS) implemented the Medicare Drug Benefit, or “Medicare Part D.” The Medicare Part D prescription drug benefit is the largest new federal entitlement program since the introduction of Medicare. There were 203 MA plans, and 1,000 beneficiaries were randomly sampled from each. The analysis was limited to beneficiaries who met the following analytic criteria:

1. Were aged 65 years or older at the time of completing the baseline survey.
2. Had enough data to calculate baseline Physical Component Summary (PCS) and Mental Component Summary (MCS) scores from the Veterans RAND 12-item health survey (VR-12) using a previously validated Modified Regression Estimation (MRE) algorithm for imputing data as well as adjustments for contextual issues such as mode of administration (phone versus mail-out). We used the PCS and MCS to calculate expected mortality rates as described below.
3. Were members of a health plan at baseline that remained in the HOS at follow-up.

We identified 188,515 beneficiaries (Figure 1). Among these 188,515 patients, 111,667 met all 3 of the above study criteria. Of the latter, we identified 94,630 who had Medicare Part D claims. Out of these, 7,148 (7.54%) had died within 2 years of follow-up.

### Study Measures

We used 2 study measures:

1. **2-year mortality rates**: Building upon prior work, we used risk-adjusted mortality as the study outcome. Mortality is a measure that is particularly relevant to elderly patients and might reflect potentially poor quality of care. We used the Medicare HOS mortality files to ascertain the vital status of the MA patients. These files were created using information from the National Center for Health Statistics mortality files that include a record for every death of a U.S. resident recorded in the United States.

2. **Performance indicators**: To evaluate performance, we assessed how well plans followed clinical practice guidelines that are nationally recognized, based on scientific evidence and expert consensus, relate to common medical conditions, and address activities that clinicians can control directly. We selected 5 high-volume diagnoses in an ambulatory care setting: diabetes, CAD, CHF, COPD/asthma and depression (Table 1). These diagnoses were self-reported in the Medicare HOS survey. This

### Table 1: Performance Indicators

<table>
<thead>
<tr>
<th>Condition</th>
<th>Performance Indicator</th>
<th>Clinical Practice Guideline/Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>ACE inhibitors/ARBs</td>
<td>ADA</td>
</tr>
<tr>
<td></td>
<td>Lipid-lowering medicines</td>
<td>ADA</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>Beta-blockers</td>
<td>ACC/AHA</td>
</tr>
<tr>
<td></td>
<td>Lipid-lowering medicines</td>
<td>ACC/AHA</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>ACE inhibitors/ARBs</td>
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</tr>
<tr>
<td></td>
<td>Beta-blockers</td>
<td>ACC/AHA</td>
</tr>
<tr>
<td></td>
<td>Lipid-lowering medicines</td>
<td>ACC/AHA</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease/asthma</td>
<td>Steroid inhalers</td>
<td>ATS</td>
</tr>
<tr>
<td>Depression</td>
<td>Antidepressant medicines</td>
<td>APA</td>
</tr>
</tbody>
</table>

ACC/AHA = American College of Cardiology/American Heart Association; ACE = angiotensin-converting enzyme inhibitor; ADA = American Diabetes Association; APA = American Psychiatric Association; ARB = angiotensin II receptor blocker; ATS = American Thoracic Society.

Data as well as adjustments for contextual issues such as mode of administration (phone versus mail-out). We used the PCS and MCS to calculate expected mortality rates as described below.

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2. **Performance indicators**: To evaluate performance, we assessed how well plans followed clinical practice guidelines that are nationally recognized, based on scientific evidence and expert consensus, relate to common medical conditions, and address activities that clinicians can control directly. We selected 5 high-volume diagnoses in an ambulatory care setting: diabetes, CAD, CHF, COPD/asthma and depression (Table 1). These diagnoses were self-reported in the Medicare HOS survey. This
method to classify conditions was validated in a previous work.

Within each of the 5 diagnoses, there were 1 to 3 drug interventions that were measured as performance indicators. There were 2 performance indicators for the diagnosis of diabetes: the percentage of patients with diabetes treated with (1) ACE inhibitors or angiotensin II receptor blockers (ARBs) and (2) lipid-lowering medications. There were 2 indicators for the diagnosis of CAD: the percentage of patients with CAD treated with (1) beta-blockers and (2) lipid-lowering medications. There were 3 indicators for the diagnosis of CHF: the percentage of patients with CHF treated with (1) ACE inhibitors or ARBs, (2) beta-blockers, and (3) lipid-lowering medications. There was 1 indicator each for the diagnoses of COPD/asthma and depression: the percentage of patients with COPD/asthma treated with steroid inhalers and the percentage of patients with depression treated with antidepressant medications. We used the Medicare Part D prescription benefit file to calculate the performance indicators. This file contains information that was collected between January 1, 2006, and December 31, 2007. We did not use National Drug Codes (NDCs) from the U.S. Food and Drug Administration because this classification scheme has not been updated since 1976. To identify the medications for each of the selected class groups, we used the Tarascon Pocket Pharmacopoeia 2009 Classic Shirt-Pocket Edition 23rd edition and followed an algorithm similar to the Healthcare Effectiveness Data and Information Set (HEDIS) 2008 NDC class assignment.

Analytic Plan

Our first objective was to profile the MA plans based on the proportion of patients treated according to clinical practice guidelines. For each selected performance indicator, we calculated the prevalence for each MA plan. The numerator was the number of patients receiving the desired drug in each MA plan. The denominator had the chronic condition for which the number of patients receiving the desired drug in each MA plan. The denominator had the chronic condition for which the number of patients receiving the desired drug in each MA plan. We used the Medicare Part D prescription benefit file to calculate the performance indicators. This file contains information that was collected between January 1, 2006, and December 31, 2007. We did not use National Drug Codes (NDCs) from the U.S. Food and Drug Administration because this classification scheme has not been updated since 1976. To identify the medications for each of the selected class groups, we used the Tarascon Pocket Pharmacopoeia 2009 Classic Shirt-Pocket Edition 23rd edition and followed an algorithm similar to the Healthcare Effectiveness Data and Information Set (HEDIS) 2008 NDC class assignment.

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Step 1: We computed propensity scores that were defined in 2 ways: (a) as the probability of a patient being on a specific drug for the analysis of individual performance indicators and (b) as the probability of a patient being on any of the eligible drugs for the analysis of multiple performance indicators. Propensity matching was employed in order to control for confounding by indication of medications and to limit as much as possible the problem of endogeneity of medications prescribed by balancing groups using covariates in the propensity score model. We used logistic regression models in which the log of the “odds” of the event was modeled as a linear function of the predictor variables. We included the following predictor variables: age, gender (male/female), race/ethnicity (whites/African Americans/Hispanics/others), married (yes/no), less than high school education (yes/no), body mass index, baseline physical functioning, baseline PCS and MCS, Activities of Daily Living questionnaire (self-care, household care, employment and recreation, shopping and money, travel, and communication), presence of medical/psychiatric conditions (diabetes, hypertension, stroke, CHF, CAD, COPD/asthma, cancer, arthritis of the hip, arthritis of the hand, low back pain, osteoporosis, sciatica, depression), shortness of breath, current smoker (yes/no).

Step 2: We generated weights from the propensity scores in step 1 by applying the Horwitz and Thompson weighting approach. This methodology provides unbiased estimates of the probability of being on treatment by comparing treatment groups within each of the stratified levels of the propensity score. The weights were defined as the total number of patients on a drug/10)/number of patients on a drug in 1 decile and the total number of patients not on a drug/10)/number of patients not on a drug. Each individual was assigned with 1 of the 2 weights in each decile.

Step 3: We calculated the expected mortality rate by applying the weights from step 2 to a probability-weighted regression model. In the model, mortality was the dependent variable and medication vs. no medication was the independent variable. The patients’ expected mortality rates for each plan were aggregated in order to calculate the plan-expected mortality rate.

In this correlation analysis, a single patient with diabetes could have as many as 2 separate correlations with mortality, 1 for each guideline, when we calculated the prevalence of the selected performance indicators for each MA plan. For example, to calculate the association between ACE/ARB and mortality, we examined all patients with diabetes who qualified for ACE/ARB. Then we repeated the analysis for all patients who qualified for lipid-lowering medications. Thus, some patients were counted twice. We also examined the association between mortality and the multiple performance indicators for
conditions such as diabetes, CAD, and CHF. We calculated composite scores of the performance indicators as the summation of the different binary performance scores at the patient level and averaged them together for each MA plan.

**Results**

**Characteristics of the Participants**

Table 2 summarizes the characteristics of the 94,630 MA patients with Medicare Part D claims. When compared with MA patients without claims (N=17,037), they were more likely to be female, nonwhite, not married, have less than a high school education, and have an income less than $20,000. The MA patients with Medicare Part D claims also had higher prevalence of chronic conditions, including diabetes (23.0% vs. 18.1%; P<0.0001), hypertension (65.9% vs. 55.1%; P<0.0001), CAD (15.7% vs. 14.6%; P=0.0003), CHF (9.3% vs. 7.9%; P<0.0001), COPD/asthma (14.4% vs. 11.8%; P<0.0001), and depression (28.6% vs. 23.0%; P<0.0001). They had lower PCS scores (39.0 [SD±12] vs. 40.8 [SD±11]; P<0.0001) and MCS scores (51.7 [SD±11] vs. 53.1 [SD±10]; P<0.0001). There was no difference in the 2-year mortality rates between patients with or without Medicare Part D claims (7.55% vs. 7.54%, respectively).

**Variation of Performance Indicators Across MA Plans**

Table 3 shows the variation across MA plans of the percentage of guideline-eligible patients who received an indicated drug. The performance indicator estimates for diabetes ranged from 53.3% to 100% for ACE inhibitors/ARBs and 33.3% to 90.0% for lipid-lowering medications. Estimates for CAD ranged from 42.4% to 100% for beta-blockers and 51.8% to 100% for lipid-lowering medications. Those for CHF ranged from 38.5% to 86.7% for ACE inhibitors/ARBs, from 33.3% to 100% for lipid-lowering medications, and from 46.7% to 93.3% for beta-blockers. The proportion of patients with diabetes receiving none, 1, or 2 recommended medications ranged from 3.3% to 33.3%, 13.1% to 46.6%, and 33.3% to 85.7%, respectively. The proportion of CAD patients receiving none, 1, or 2 recommended medications ranged from 0% to 33.3%, 0% to 50.0%, and 29.8 to 100%, respectively. The proportion of CHF patients receiving none, 1, 2, or 3 recommended medications ranged from 0% to 28.5%, 0% to 100%, 11.5% to 57.5%, and 14.2% to 63.6%, respectively. The performance indicator for COPD/asthma ranged from 21.3% to 71.4% for inhaled steroids. Last, for depression, the performance indicator ranged from 7.4% to 66.7% for antidepressant medications. Analysis of variance confirmed that the achievement of guideline-recommended treatment differed significantly across the 203 MA plans (P<0.02).

**Associations Between Mortality and Variation in Guideline-Recommended Medications Across MA Plans**

Table 3 shows that there were significant associations between O/E mortality ratios and the use of guideline-recommended medications across MA plans. In patients with CHF, those plans with higher use of ACE inhibitors/ARBs (r=-0.40; P<0.0001) and beta-blockers (r=-0.27; P<0.0001) had significantly lower O/E mortality ratios, and the association with the use of lipid-lowering medications was close to statistical significance (r=-0.11; P=0.091). Those MA plans with higher composite scores for use of multiple guideline-recommended medications in CHF had significantly lower O/E mortality ratios (r=-0.45; P<0.0001). The findings for diabetes were similar. Those MA plans with higher composite scores had significantly lower O/E mortality ratios (r=-0.14; P<0.042). There were no significant associations between performance indicators and mortality in CAD or COPD/asthma. Antidepressant medications showed a paradoxical correlation. Those MA plans with higher use of antidepressant medications had significantly higher O/E mortality ratios (r=0.28; P<0.0001).
in its scoring of plans and is also linked to reimbursement and bonuses. The challenge is evident in the wide variation that we found in the prescription of guideline-recommended medications. The consequence is revealed by the association of guideline-discordant care with increased mortality among patients with CHF and diabetes. Future efforts should focus on identifying factors that account for plan variation in the prescription of guideline-recommended medications and on remedial quality improvement activities (standing orders, reminder systems, critical care pathways, algorithms, audits).

The observed variation across MA plans in guideline-recommended care poses a serious threat to the health and well-being of patients. Mortality is but the most severe consequence of deviation from guidelines that can benefit other outcomes as well. Guideline adherence will become even more critical as the population of older persons with chronic conditions increases. A key component of any solution will be the routine availability of information on quality of care. This study has shown the value of both risk-adjusted mortality rates and Medicare Part D for providing information that can help to focus efforts to improve the quality of health care delivery.

Our findings confirm the expected relationship between the selected performance indicators and patient survival. Plans’ adherence to guideline-recommended medications was associated with decreased mortality in CHF. This conforms to literature showing that the use of ACE inhibitors and beta-blockers lowers mortality by 31% and 35% in 1 year, respectively. There is, however, conflicting data regarding the mortality benefit of lipid-lowering medications in patients with established CHF, and this corresponds to our finding of equivocal benefit. Our findings also suggest that there are greater effects with multiple coexisting performance indicators in conditions such as CHF and diabetes. The summation of the coexisting guideline-recommended medications was associated with better survival.

There was a paradoxical relationship between the use of antidepressants and mortality. A steadily increasing body of literature continues to document an association between depression and mortality in elderly populations. We cannot state that higher use of antidepressant medications was the cause of higher mortality across plans. It may be that the use of antidepressants is a marker for worse depression. Severe depression has been associated with decreased self-care, which may not be completely addressed by treatment.

We found no significant association between variation in the prescription of guideline-recommended medications and mortality in patients with CAD and COPD/asthma. This may be because the treatment effect is small in COPD or because it is tempered by other aspects of care in CAD, such as coronary bypass grafting. In addition, we measured all-cause mortality, so detrimental effects of suboptimal treatment for our study conditions may have been counterbalanced by good treatment for other conditions. Last, we may have needed a larger number of patients and/or longer follow-up to detect the effect of guideline-recommended medications on mortality.

### TABLE 3

<table>
<thead>
<tr>
<th>Condition</th>
<th>2-Year Mortality Rates Range</th>
<th>Performance Indicator</th>
<th>Performance Indicator Range</th>
<th>Correlation with O/E Mortality Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>0%–20%a</td>
<td>ACE inhibitors/ARBs</td>
<td>53.3%–100%a</td>
<td>-0.07 (P = 0.294)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lipid-lowering medications</td>
<td>33.3%–90.0%a</td>
<td>-0.09 (P = 0.199)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No performance indicator</td>
<td>3.3%–33.3%a</td>
<td>-0.14 (P = 0.042)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 performance indicator</td>
<td>13.1%–46.6%a</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 performance indicators</td>
<td>33.3%–85.7%a</td>
<td></td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>0%–25%a</td>
<td>Lipid-lowering medications</td>
<td>51.8%–100%a</td>
<td>0.06 (P = 0.352)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Beta-blockers</td>
<td>42.4%–100%a</td>
<td>-0.07 (P = 0.257)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No performance indicator</td>
<td>0%–33.3%a</td>
<td>-0.06 (P = 0.365)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 performance indicator</td>
<td>0%–50.0%a</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 performance indicators</td>
<td>29.8%–100%a</td>
<td></td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>0%–100%a</td>
<td>ACE inhibitors/ARBs</td>
<td>38.5%–86.7%a</td>
<td>-0.40 (P &lt; 0.0001)</td>
</tr>
<tr>
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<td></td>
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<td>33.3%–100%a</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>Beta-blockers</td>
<td>46.7%–93.3%a</td>
<td>-0.27 (P &lt; 0.0001)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No performance indicator</td>
<td>0%–28.5%a</td>
<td>-0.45 (P &lt; 0.0001)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 performance indicator</td>
<td>0%–100%a</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 performance indicators</td>
<td>11.5%–57.5%a</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 performance indicators</td>
<td>14.2%–63.6%a</td>
<td></td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease/Asthma</td>
<td>0%–27.3%a</td>
<td>Inhaled steroids</td>
<td>21.3%–71.4%a</td>
<td>0.036 (P = 0.608)</td>
</tr>
<tr>
<td>Depression</td>
<td>2.1%–23.1%a</td>
<td>Antidepressants</td>
<td>7.4%–66.7%a</td>
<td>0.28 (P &lt; 0.0001)</td>
</tr>
</tbody>
</table>

aAnalysis of variance showed that the 203 plans differed significantly (P ≤ 0.02). ACE inhibitors = angiotensin-converting enzyme inhibitors; ARBs = angiotensin II receptor blockers; O/E = observed/expected.

### Discussion

The importance of providing care that is in accord with accepted guidelines is enhanced by the aging of the U.S. population and the corresponding increase in the prevalence of chronic disease. In fact, the relatively new Medicare Part D Star Ratings incorporates medication adherence to guidelines...
Limitations
There are several limitations of this study. First, we found that 15.2% of the HOS patients did not have Part D Medicare claims. There are several possibilities regarding these patients: (a) they might not be enrolled in the Part D program, (b) they might be enrolled but not using medications, (c) they might have other prescription coverage (e.g., a company’s retirement insurance), and (d) they might have missing information. Second, the Medicare Part D claim file does not contain drug class assignment. We compared our drug class algorithm with the HEDIS 2008 NDC class assignment. We found that both algorithms produced similar results (data not shown). Third, we did not have disease severity measures. However, we used measures of illness burden such as the PCS and MCS in our analysis. Fourth, we were unable to incorporate contraindications, drug interaction, and allergy. Those patients for whom the drug may be contraindicated were not excluded from the denominator. A more accurate count of patients receiving the desired drug could be made if patient allergies were to become listed in the Medicare Part D file. Fifth, deviation from guideline-recommended prescriptions might be due to specific situations, which are unique to elderly patients, such as presence of multiple conditions and polypharmacy. Older patients with comorbidities might require multiple medication use, which may ameliorate symptoms and improve or preserve quality of life. Unfortunately, multiple medication use is also a major risk factor for prescribing and adherence problems, adverse drug events, and other adverse health outcomes. Sixth, we have not taken into account the number of guidelines satisfied across conditions (e.g., patients who have diabetes plus CHF) due to sample-size limitations. Seventh, we did not examine the effect of the “doughnut hole” on clinical outcomes. Among Medicare Part D enrollees in 2007 who were not eligible for the low-income subsidies, 26% had spending high enough to reach the coverage gap. “Between 2007 and 2017, the dollar value of the coverage gap is projected to double, exposing some beneficiaries to potentially high out-of-pocket costs and increasing the risk of cost-related noncompliance.” Eighth, assumptions made about individuals based on aggregate data are vulnerable to the ecological fallacy. This does not mean that identifying associations between aggregate figures is necessarily defective, and it doesn’t necessarily mean that any inferences drawn about associations between the characteristics of an aggregate population and the characteristics of subunits within the population are absolutely wrong either. What it does say is that the process of aggregating or disaggregating data may conceal the variations that are not visible at the larger aggregate level. Last, the use of propensity scores for balancing the medication groups controls the confounding by indication; however, this method does not eliminate the problems of endogeneity.

Conclusions
In summary, elderly patients are a fragile group with higher mortality when not treated according to clinical practice guidelines. Our results are the first to indicate that there is substantial variation across MA plans in the prescription of guideline-recommended medications and that this variation correlates with differences in patient survival. These findings can serve to both motivate and help target quality improvement programs.

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All authors contributed to the concept and design, data collection, data interpretation, writing and revision of this article.

REFERENCES
Management of Familial Hypercholesterolemia: A Review of the Recommendations from the National Lipid Association Expert Panel on Familial Hypercholesterolemia

Jennifer G. Robinson, MD, MPH

SUMMARY

Familial hypercholesterolemia (FH) is a genetic disorder of lipid metabolism that is characterized by a significant elevation in levels of low-density lipoprotein cholesterol (LDL-C), and patients are at very high risk for premature coronary heart disease (CHD). The etiology of FH includes known mutations in the gene of the LDL receptor, LDLR; the gene of apolipoprotein B, apo B; and the proprotein convertase subtilisin/kexin type 9 gene, PCSK9. The National Lipid Association Expert Panel on Familial Hypercholesterolemia has provided recommendations for the screening and treatment of patients with FH. Early identification and aggressive treatment of FH in individual patients, as well as screening of all first-degree relatives, are recommended to minimize the risk for premature CHD. Similar to patients with conventional hypercholesterolemia, patients with FH should receive statins as initial treatment, but patients with FH may require higher doses of statins, more potent statins, statin-based combination therapy, or adjunctive therapies. Patients with FH who have additional risk factors for, or existing, cardiovascular disease or those with an inadequate response to initial statin therapy should have access to higher doses of the most efficacious statins; statins used in combination with other LDL-C–lowering agents should also be supported by formularies; additional treatments, such as LDL-C apheresis or novel therapies, may also be required to achieve acceptable LDL-C levels. New treatment approaches include mipomersen, which was approved by the FDA in January 2013. Mipomersen is an oligonucleotide inhibitor of apolipoprotein B-100 synthesis (called an antisense inhibitor) indicated as an adjunct to lipid-lowering medications and diet to reduce LDL-C, apolipoprotein B, total cholesterol, and non-high density lipoprotein-cholesterol (non-HDL-C) levels in patients with homozygous FH (HoFH). The microsomal transfer protein lomitapide has also received FDA approval for use only in patients with HoFH. Other novel treatments currently in development include PCSK9 inhibitors. Therapies such as apheresis are likely more expensive than simple therapy with a statin but may be needed to achieve long-term reductions in complications from nonfatal and fatal cardiovascular events and hospitalizations related to myocardial infarction, cardiac revascularization, and stroke in FH patients. The cost-effectiveness of this more aggressive therapy has not been determined and should be studied. Utilization of published guidelines and the recommendations from the National Lipid Association will help to optimize the management of patients with FH.

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Individuals with familial hypercholesterolemia (FH) are at significantly increased risk for premature cardiovascular disease (CVD). Patients with FH generally have significantly higher levels of low-density lipoprotein cholesterol (LDL-C) than most patients with severe hyperlipidemia. Patients with FH older than 30 years of age often have an LDL-C level of 250 milligrams per deciliter (mg/dL) or higher; patients between 20 and 29 years of age often have an LDL-C level of 220 mg/dL or higher; and those younger than 20 often have an LDL-C level of 190 mg/dL or higher.1 Patients with FH may have thickening of the tendons called tendon xanthomas. Because FH is primarily an autosomal dominant disorder, family members of a person with FH may manifest a bimodal distribution of LDL-C.1 FH is a disorder of LDL-C metabolism and may be the most common serious genetic disorder, with an estimated 620,000 individuals affected in the United States.1,2 Heterozygous FH (HeFH) is the most common form of the disease (prevalence of approximately 1 in 300 to 500 persons worldwide and as high as 1 in 100 persons in some populations), with the majority of inheritance through an autosomal-dominant mechanism.1-4 Homozygous FH (HoFH) is a very rare form of the disease (prevalence of 1 in 1 million persons). Some populations, such as French Canadians, Ashkenazi Jews, Lebanese, and Dutch Afrikaners, are at a higher risk for FH owing to an increased prevalence of FH-associated mutations in the LDL receptor gene, LDLR, in these founder populations.1-5,8 FH is characterized by severe hypercholesterolemia that results in premature CVD. Individuals with FH are at increased risk for cardiac events such as premature myocardial infarction and early death from premature coronary heart disease (CHD) especially in patients with severe forms of the disease if left untreated.2,9,10 HeFH is characterized by 1 normally functioning gene and is less severe and more responsive to treatment such as statins than HoFH. The mean age for the onset of CVD in men with HeFH is 42 to 46 years and in women, onset is 51 to 52 years.11,12 HoFH is a severe, aggressive form of FH, which is often unresponsive to traditional treatment for hypercholesterolemia owing to the patient’s lack of functional LDL receptors.10,12 In patients with HoFH, the mean age at the time of diagnosis of CVD is 20 years.9 More than 85% of FH cases are due to inherited mutations in the LDLR gene, with more than 1,600 mutations identified.1 Mutation of the LDLR gene leads to defective uptake of LDL-C.
from the blood. Less commonly, FH may also be caused by mutations in the gene encoding apolipoprotein B (apo B), the proprotein convertase subtilisin/kexin type 9 (PCSK9) gene, or rare mutations in the LDLRAP1 gene. Apo B is important for lipid metabolism because serum lipoproteins, including LDL-C and very low-density lipoprotein (VLDL), contain apo B as a structural component. The level of apo B correlates with cardiovascular risk. Apo B is also necessary for transport of VLDL from the liver into the plasma. PCSK9 is a convertase enzyme that mediates the degradation of the LDL receptor. The importance of PCSK9 is shown by significantly lower LDL-C levels and incidence of CHD in patients with nonsense mutations in the PCSK9 gene. The LDLRAP1 gene encodes an adaptor protein for trafficking of LDL receptors in cells in the liver, and mutations have been identified in patients with either FH, an autosomal dominant disorder, or an autosomal recessive hypercholesterolemia.

Elevations in LDL-C levels are a function of the severity of the genetic mutation and whether it is homozygous or compound heterozygous. When left untreated, patients with HeFH typically have 2- to 3-fold higher levels of plasma LDL-C compared with healthy individual (about 200-400 mg/dL), whereas patients with HoFH have levels of LDL-C that are 6- to 10-fold higher than normal (> 600 mg/dL).

Patients should initiate positive modifications to their lifestyle; however, drug therapy is almost always required to decrease LDL-C to the desired levels to reduce the risk of premature CVD. Even though many patients with FH are treated using the current standard of care for hyperlipidemia, patients with FH should receive aggressive statin therapy to achieve more than a 50% reduction in LDL-C levels, which usually requires high doses of high-potency statins. In patients with other forms of severe hyperlipidemia or FH with clinical CVD, diabetes, or additional risk factors, treatment should be intensified to decrease LDL-C levels to less than 100 mg/dL, if possible, according to the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATP III) guidelines and reiterated in the National Lipid Association (NLA) FH Treatment statement. LDL-C levels of less than 100 mg/dL have been identified as the treatment target for cholesterol-lowering therapy in patients at higher risk for CVD.

A need exists for the increased awareness of early, aggressive treatment of patients with FH to prevent or slow the progression of CVD caused by exposure to high lipid levels since birth. From a pharmacy perspective of the management of FH, high-dose statins and adjunctive LDL-C-lowering therapies need to be available on insurance and managed care formularies, with reduced copayments for patients with FH in order to improve utilization. Eliminating copayments has been shown to increase adherence to generic statin therapy. Decreasing or eliminating copayments would likely increase the use of statins or adjunctive therapies in patients with FH. Although statins are generally inexpensive, adjunctive therapies such as other LDL-C–lowering drugs and apheresis can be expensive and come with high patient out-of-pocket contributions.

This review includes management options for FH and highlights the recommendations from the NLA Expert Panel on Familial Hypercholesterolemia regarding the need for early and aggressive treatment.

### Risk Factors for Cardiovascular Disease in Familial Hypercholesterolemia

Risk factors for CVD in patients with FH are similar to those in patients without FH, although FH itself is a significant CVD risk factor because it results in long-term exposure to high lipid levels. Increasing age, elevated levels of total cholesterol and LDL-C, low levels of high-density lipoprotein cholesterol (HDL-C), male sex, smoking, metabolic syndrome, diabetes, hypertension, and a family history of early CVD are risk factors for developing CVD. These factors accelerate the development of atherosclerosis in patients with and without FH and must be treated aggressively, especially in those with FH. Smoking is an extremely important andmodifiable risk factor in patients with FH, and smoking must be avoided due to the increased likelihood of developing very premature onset of CVD. Additional factors that may put patients with FH at increased risk for CVD include lipoprotein(a) (Lp[a]) levels of 50 mg/dL or higher and the presence of 2 or more CVD risk factors.

Risk stratification algorithms are often used to identify candidates for drug therapy on the basis of estimated CVD risk. However, risk stratification algorithms, such as the Framingham equations recommended by ATP III, underestimate the 10-year risk of CHD in patients with FH because of their lifelong exposure to severely elevated LDL-C levels. Therefore, risk stratification should not be used in patients with FH, who are already candidates for drug therapy on the basis of their genetic disorder. Patients with severe HeFH and clinical CVD and those with HoFH are at very high CVD risk and require intensive LDL-C–lowering therapy.

### Management Objectives for Patients with Familial Hypercholesterolemia

Early treatment of FH is highly beneficial for reducing CVD events. According to NLA treatment recommendations, the goal of treatment in adults with FH is to achieve a 50% or greater decrease in LDL-C levels with statin therapy. Patients with FH who are at a higher risk for CVD—including those with clinically evident CVD or atherosclerotic disease, diabetes, family history of early CVD, current smoking, 2 or more CVD risk factors, or an Lp(a) level of 50 mg/dL or higher—should be treated in an effort to achieve an LDL-C level of less than 100 mg/dL. The highest doses of high-potency statins may be needed to achieve this reduction in LDL-C levels. For
Management of Familial Hypercholesterolemia: A Review of the Recommendations from the National Lipid Association Expert Panel on Familial Hypercholesterolemia

**TABLE 1** National Lipid Association Screening Recommendations

- Universal screening for elevated serum cholesterol is recommended. FH should be suspected when untreated fasting LDL-C or non-HDL-C levels are at or above the following:
  - Adults (age ≥ 20 years): LDL-C ≥ 190 mg/dL or non-HDL-C ≥ 220 mg/dL
  - Children, adolescents, and young adults (age < 20 years): LDL-C ≥ 160 mg/dL or non-HDL-C ≥ 190 mg/dL

- For all individuals with these levels, a family history of high cholesterol and heart disease in first-degree relatives should be collected. The likelihood of FH is higher in individuals with a positive family history of hypercholesterolemia or of premature CHD (onset in men aged < 55 years and women aged < 65 years).

- Cholesterol screening should be considered beginning at age 2 for children with a family history of premature CVD or elevated cholesterol levels. All individuals should be screened by age 20.

- Although not present in many individuals with FH, the following physical findings should prompt the clinician to strongly suspect FH and obtain necessary lipid measurements, if not already available:
  - Tendon xanthomas at any age (most common in Achilles tendon and finger extensor tendons but can also occur in patellar and triceps tendons)
  - Arcus corneae in patients aged < 45 years
  - Tuberous xanthomas or xanthelasmas in patients aged < 20 years

- At the LDL-C levels listed below, the probability of FH is approximately 80% in the setting of general population screening. These LDL-C levels should prompt the clinician to strongly consider a diagnosis of FH and obtain further family information:
  - LDL-C ≥ 250 mg/dL in patients aged ≥ 30 years
  - LDL-C ≥ 220 mg/dL in patients aged 20 to 29 years
  - LDL-C ≥ 190 mg/dL in patients aged < 20 years

- The NLA recommends that cascade screening, a process for identifying family members at risk for a genetic condition, should be performed in all first-degree relatives of patients with FH for the early diagnosis and prevention of CVD in family members.23 Cascade screening has been shown to have an LDL-C level of at least 160 mg/dL (or a non-HDL-C level of at least 190 mg/dL), other LDL-C–lowering therapies should be added.5 Similarly, multiple LDL-C–lowering therapies will typically be required in patients with FH at highest risk for CHD to achieve the more aggressive goal for LDL-C levels of less than 100 mg/dL and the goal for non-HDL-C levels of less than 130 mg/dL.36 HDL-C is not considered a target for therapy in these patients.56,38

**TABLE 2** Criteria for Total Cholesterol and Low-Density Lipoprotein Cholesterol for the Diagnosis of Probable Heterozygous Familial Hypercholesterolemia (HeFH)*

<table>
<thead>
<tr>
<th>Ages</th>
<th>First-Degree Relative</th>
<th>Second-Degree Relative</th>
<th>Third-Degree Relative</th>
<th>General Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 18 years</td>
<td>220 (155)</td>
<td>230 (165)</td>
<td>240 (170)</td>
<td>270 (200)</td>
</tr>
<tr>
<td>20-29 years</td>
<td>240 (170)</td>
<td>250 (180)</td>
<td>260 (185)</td>
<td>290 (220)</td>
</tr>
<tr>
<td>30-39 years</td>
<td>270 (190)</td>
<td>280 (200)</td>
<td>290 (210)</td>
<td>340 (240)</td>
</tr>
<tr>
<td>≥ 40 years</td>
<td>290 (205)</td>
<td>300 (215)</td>
<td>310 (225)</td>
<td>360 (260)</td>
</tr>
</tbody>
</table>

Adapted from Williams RR, Hunt SC, Schumacher MC, et al. Diagnosing heterozygous familial hypercholesterolemia using new practical criteria validated by molecular genetics.58

*Total cholesterol levels in milligram per deciliter (low-density lipoprotein cholesterol levels in parentheses) expected to diagnose HeFH with 98% specificity. First-degree relatives are parents, offspring, brothers, and sisters; second-degree relatives are aunts, uncles, grandparents, nieces, and nephews; third-degree relatives are first cousins and siblings of grandparents.

those who do not achieve at least a 50% reduction in LDL-C levels with maximally tolerated statin therapy or who continue to have an LDL-C level of at least 160 mg/dL (or a non-HDL-C level of at least 190 mg/dL), other LDL-C–lowering therapies should be added.5 Similarly, multiple LDL-C–lowering therapies will typically be required in patients with FH at highest risk for CHD to achieve the more aggressive goal for LDL-C levels of less than 100 mg/dL and the goal for non-HDL-C levels of less than 130 mg/dL.36 HDL-C is not considered a target for therapy in these patients.56,38

**Screening and Diagnosis**

Early identification of FH is best achieved by the initiation of screening between the ages of 9 and 11 years in children and no later than 20 years in adults (Table 1).3,24 In families with a history of FH or premature-onset CHD, screening should begin at age 2 years.3 Formal diagnosis of FH is made by using 1 of several validated criteria, including the U.S. Make Early Diagnosis Prevent Early Death (MEDPED; Table 2), the Dutch Lipid Clinic Network, and the Simon Broome Registry.3,39 A family history of 2 or more family members with elevated LDL-C levels, along with a family history of pediatric cases of FH, or the presence of tendon xanthomas in the patient or a first-degree relative permit a clinical diagnosis.5 Physical signs of the disease are often specific but not exclusive to FH, including tendon xanthomas and corneal arcs, although their absence does not rule out a diagnosis of FH.3

The NLA recommends that cascade screening, a process for identifying family members at risk for a genetic condition, should be performed in all first-degree relatives of patients with FH for the early diagnosis and prevention of CVD in family members.4,61 In cascade screening, all first-degree relatives of a patient diagnosed with FH undergo lipid screening for evidence of FH.1,60,61 The probability of detecting FH in first-degree relatives of these patients is 50%; the probability in second-degree relatives is 25%; and the probability in third-degree relatives is 12.5%.1,60,61 The cascade effect comes from the subsequent screening of all first-degree relatives from patients with FH identified in the initial testing with continuing spread of the testing to additional first-degree relatives as each patient is diagnosed with FH.23 Cascade screening has been shown to be cost-effective in identifying additional patients with FH.42,43 The United Kingdom National Institute for Health and Clinical Excellence (NICE) guidelines also recommend the use of cascade screening as a diagnostic tool, along with DNA testing and cholesterol measurement.49 The NLA guidelines summarized in this review do not require genetic testing or DNA testing for a diagnosis of FH or selection of treatment, but genetic testing can be used if the diagnosis is uncertain.3,3

**Therapeutic Options**

Patients with FH should adopt lifestyle modifications, including a healthy diet, exercise, weight control, blood pressure...
control, and smoking cessation. Similarly, the NICE guidelines recommend lifestyle modifications and smoking cessation. A number of drug treatment options are available for FH. The increased risk for CVD and unique treatment needs of these patients may require managed care organizations to offer expanded formulary options, including allowing the highest doses of statins, more potent statins, newly approved drugs, and unique combination therapies.

Statins should be the first-line therapy for patients with FH, according to the NLA recommendations, the NCEP ATP III guidelines, and the NICE guidelines. Low-potency statins are generally inadequate to reduce LDL-C levels by 50% or greater in patients with FH (Table 3). In a comparative dose efficacy study, a moderate dose of a higher-potency statin (atorvastatin 10 mg and 20 mg) was more efficacious than lower-potency statins (simvastatin, pravastatin, lovastatin, or fluvastatin) in patients with hypercholesterolemia yet still did not lower LDL-C levels by 50% or more. Therefore, even higher doses of high-potency statins are often needed in patients with FH. A review of clinical trials of high-dose statins in coronary artery disease reported that, compared with moderate-dose statins, high-dose statins reduced the death rate due to coronary death or myocardial infarction by 16%, and in patients with acute coronary syndrome, high-dose statins decreased the risk of all-cause mortality by 22% and of cardiovascular mortality by 25% over treatment periods of 2 to 5 years. One study showed that in patients with FH, moderate-dose statins reduced the risk for CVD by up to 80%. High-dose statins are generally well tolerated. In large, long-term clinical trials in secondary prevention in patients with hyperlipidemia, but not specifically FH, atorvastatin 80 mg was efficacious and was associated with low rates of serious adverse musculoskeletal (<0.6%) and hepatic (<1.3%) events. Rosuvastatin 20 mg was used over a shorter period in a large primary prevention population and was also associated with very low rates of serious muscle and liver adverse events. Fewer long-term data are available for rosuvastatin 40 mg. In contrast, 1.4% of patients receiving simvastatin 80 mg in the Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) trial developed myopathy compared with 0.2% of patients receiving simvastatin 20 mg in the placebo group; however, clinicians are advised to be aware of the potential increased risk for muscle injury according to a U.S. Food and Drug Administration (FDA) advisory from March 2010. High-dose statins are associated with a somewhat higher rate of discontinuation, ranging from 3.2% to 9.6% due to drug-related adverse events. High-dose statins are, therefore, a well-tolerated treatment option for the large majority of high risk patients. The main question about the long-term safety of high-intensity statins arises from the increased risk for type 2 diabetes with these agents. High-intensity statins increase the risk for diabetes in those with increasing numbers of risk factors. For individuals with FH, diabetes risk factors markedly increase CVD risk, as previously discussed. However, analyses have not been performed to estimate the trade-offs in terms of long-term CVD risk reduction compared with the risk of diabetes complications.

### TABLE 3: Differing Efficacies of Statins Based on Their Abilities to Decrease LDL-C Levels

<table>
<thead>
<tr>
<th>Statin/Decreased LDL-C Level By:</th>
<th>30%-40%</th>
<th>&gt;50%</th>
<th>&gt;60%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin 10 mg</td>
<td>Atorvastatin 40-80 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluvastatin 80 mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lovastatin 40-80 mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pitavastatin 2-4 mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pravastatin 40-80 mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rosuvastatin 5-10 mg</td>
<td>Rosuvastatin 20 mg</td>
<td>Rosuvastatin 40 mg</td>
<td></td>
</tr>
<tr>
<td>Simvastatin 20-40 mg</td>
<td>Simvastatin/ezetimibe 20-40 mg/10 mg</td>
<td>Simvastatin/ezetimibe 80/10 mg</td>
<td></td>
</tr>
</tbody>
</table>

*Data from package inserts. LDL-C = low-density lipoprotein cholesterol; milligram = mg.

### TABLE 4: Alternative Treatment Options to Reduce LDL-C, Non-HDL-C, or apo B Levels in Patients with Familial Hypercholesterolemia Unresponsive to Initial Statin Therapy

<table>
<thead>
<tr>
<th>Drug</th>
<th>Changes in Levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C</td>
<td>Non-HDL-C</td>
</tr>
<tr>
<td>Double statin dose</td>
<td>-6% to -7%</td>
</tr>
<tr>
<td>Ezetimibe*</td>
<td>-19% to -20%</td>
</tr>
<tr>
<td>ER niacin 2 g</td>
<td>-14%</td>
</tr>
<tr>
<td>Bile acid-binding agents</td>
<td>-15% to -18%</td>
</tr>
</tbody>
</table>

*Ezetimibe in combination with statin therapy.

**Adapted from Robinson JG. Management of complex lipid abnormalities with a fixed dose combination of simvastatin and extended release niacin.**

**Moga C, Hastall C. Low density lipoprotein apheresis for the treatment of familial hypercholesterolemia.**

**Stoffel W, Bosberg H, Greve V. Application of specific extracorporeal removal of low density lipoprotein in familial hypercholesterolaemia.**

**Thompson GR. LDL apheresis.**


**Ezetimibe in combination with statin therapy.**

**Coleselvam 6 tablets (3.75 g/suspension, 3.75 g packet once daily, or 1.875 g packet twice daily).**

**apo B = apolipoprotein B; ER = extended release; g = gram; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; mg = milligram.**
For those patients with FH who are unable to tolerate statins at the highest intensity, or who are completely intolerant to statins, access to alternative LDL-C–lowering therapies is needed. Several non-statin LDL-C–lowering agents are available (Table 4).

Ezetimibe, combined with statins, such as atorvastatin and simvastatin, significantly reduces LDL-C levels by an additional 17% to 23% compared with a statin alone. Depending on the dose of statin, the addition of ezetimibe, which inhibits absorption of cholesterol from the intestine, can reduce LDL-C levels by approximately 43% to 70% in patients with HeFH and by 21% (a difference of approximately 14% from statins) in patients with HoFH. In several studies, the addition of ezetimibe to statin therapy was well tolerated, with a rate of adverse events similar to that for statin therapy alone, although statin-ezetimibe therapy more frequently causes persistent elevations in hepatic transaminase levels compared with moderate-dose statin monotherapy. The combination of simvastatin-ezetimibe has been shown to reduce CVD events compared with placebo, but the incremental CVD risk reduction benefit of adding ezetimibe to statin therapy has yet to be determined.

The bile acid sequestrant cholestyramine has been shown to reduce the risk for CVD in severely hypercholesterolemic patients. Cholestyramine and colestipol have gastrointestinal adverse effects, such as constipation; the newer bile acid sequestrant, colesevelam, is generally better tolerated with fewer drug interactions. In a phase 4 trial of 86 patients with FH, the addition of colesevelam to combination therapy with ezetimibe and a statin significantly lowered LDL-C levels by an additional 12% at 12 weeks compared with ezetimibe or a statin alone. No significant differences in adverse events were observed between the colesevelam treatment and control arms. Cholestyramine monotherapy has been shown to reduce CVD events in a primary prevention population of men with severe hypercholesterolemia, however, no CVD outcomes data are available for bile acid sequestrants combined with statin therapy.

Niacin combined with statins is a safe and effective LDL-C–lowering therapy in patients with severe hypercholesterolemia but has not been tested in clinical trials exclusively enrolling patients with FH or in combination with high-dose statins. Other than LDL-C apheresis, niacin is the only known therapy that has a significant impact on Lp(a) levels, although the clinical impact of lowering Lp(a) levels with niacin has not been established. A dose of 1.5 grams (g) to 2 g of niacin is typically required to achieve a 15% lowering of LDL-C levels; however, the efficacy and safety of these high doses in combination with high-dose statins has not been evaluated. Patients receiving high doses of niacin often experience intolerable flushing and are likely to discontinue treatment, making the use of high doses of niacin difficult to apply in clinical practice. In a review of niacin and moderate-dose statin combination therapy in hyperlipidemic patients, reductions in LDL-C levels ranging from 25% to 57% and Lp(a) levels of 37% were reported. In this analysis of 293 patients, no cases of myopathy and minimal hepatic toxicity were reported; however, 53% and 42% of patients experienced elevations in alanine aminotransferase and aspartate aminotransferase levels, respectively. The percentage of patients experiencing flushing was not reported. In another review of 4 clinical trials evaluating extended-release niacin 1,000 to 2,000 mg and simvastatin 20 mg to 80 mg, this combination lowered LDL-C levels, with reductions ranging from 2% to 24% and reductions in Lp(a) levels from 0% to 29%. The combination was well tolerated, with liver and muscle toxicities similar to those of niacin and simvastatin monotherapies. Although cutaneous adverse effects may limit the use of niacin in some patients, adherence to therapy can be improved with extended-release niacin. Extended-release niacin is contraindicated in patients with active liver disease or unexplained hepatic dysfunction, and the dose should not exceed 2 g daily due to concerns about hepatotoxicity.

Niacin monotherapy has been shown to reduce CVD events in men with CHD. Niacin when combined with simvastatin has been shown to reduce CVD risk similar to simvastatin (plus ezetimibe) when similar levels of LDL-C of about 70 mg/dL were achieved. In addition, a recent trial of niacin combined with laropiprant did not demonstrate an incremental reduction in CVD events when added to statin therapy.

**Therapeutic Options for Patients with Severe LDL-C Elevations on Maximal Drug Therapy**

Ideally, patients who have high lipid levels that are difficult to control or who are at high risk for cardiac complications should be referred to a lipid specialist. Regardless of aggressive lipid management, some patients with severe HeFH (LDL-C levels of 200 mg/dL or higher, either after maximum tolerated lipid-lowering therapy or with evidence of CVD) and the majority of patients with HoFH will not achieve sufficient reductions in LDL-C levels even with the maximal doses of statin and non-statin therapies. These patients often require additional therapy such as LDL-C apheresis (Table 4). LDL-C apheresis is an effective way to lower LDL-C levels in patients with FH who are not responsive to or are intolerant of drug therapy. Unlike statins, apheresis also lowers Lp(a) levels. Apheresis is a procedure to physically remove plasma lipoproteins from the blood using dextran sulfate cellulose adsorption (DSA), heparin-induced extracorporeal LDL cholesterol precipitation (HELP), immunoadsorption, double filtration plasmapheresis (DFPP), or direct adsorption of lipoproteins. Unfortunately, many patients with FH do not achieve the desired reduction of lipoproteins with apheresis and with all methods of removing the LDL, and the LDL-C levels return to pre-treatment levels within 2 to 4 weeks.

Apheresis and statins may effectively be combined to lower LDL-C levels in patients with HeFH as well as in those with...
Table 5
National Lipid Association Recommendations for Identifying Candidates for LDL Apheresis

LDL apheresis is an FDA-approved medical therapy for patients who are not at LDL cholesterol treatment goal or who have ongoing symptomatic disease. In patients who, after 6 months, do not have an adequate response to maximum tolerated drug therapy, LDL apheresis is indicated according to these guidelines:

1. Functional homoygous FH patients with LDL cholesterol ≥ 300 mg/dL (or non-HDL cholesterol ≥ 330 mg/dL).
2. Functional heterozygous FH patients with LDL cholesterol ≥ 300 mg/dL (or non-HDL cholesterol ≥ 330 mg/dL) and 0-1 risk factors.
3. Functional heterozygous FH patients with LDL cholesterol ≥ 200 mg/dL (or non-HDL cholesterol ≥ 230 mg/dL) and high risk characteristics such as ≥ 2 risk factors or high lipoprotein (a) ≥ 50 mg/dL using an isoform insensitive assay.
4. Functional heterozygotes with LDL cholesterol ≥ 160 mg/dL (or non-HDL cholesterol ≥ 190 mg/dL) and very high risk characteristics (established CHD, other cardiovascular disease, or diabetes).

Adapted from Ito MK, McGowan MP, Moriarty PM. Management of familial cholesterolemias in adult patients. CHD = coronary heart disease; FDA = U.S. Food and Drug Administration; FH = familial hypercholesterolemia; HDL = high-density lipoprotein; LDL = low-density lipoprotein; mg/dL = milligram per deciliter.

HoFH. In a study of 7 patients with HoFH, the combination of apheresis and atorvastatin 80 mg produced on average a 31% additional reduction in LDL-C levels over apheresis alone. In a prospective, 10-year follow-up study of 18 patients receiving the combination of apheresis and statin therapy, a delay was observed in the progression of coronary artery disease, with evidence for the prevention of major cardiac events. Little change was observed in coronary stenosis and ejection fraction. However, the use of apheresis is limited by high cost, difficult access, and the inconvenience of treatment (> 3 hours required for treatment every 1-2 weeks). The yearly cost of LDL apheresis has been estimated at $45,000 to $100,000. An estimated 400 patients receive apheresis in the United States; however, access remains a challenge, with only approximately 40 centers providing care. The number of patients who qualify and may benefit from this treatment is thought to be significantly higher. The FDA has approved LDL-C apheresis for patients with HoFH and an LDL-C level greater than 500 mg/dL and in patients with HeFH after failing a 6-month trial of diet therapy and maximally tolerated combination drug therapy and either an LDL-C level higher than 300 mg/dL without CVD or an LDL-C level higher than 200 mg/dL with known CVD. Insurers may choose other guidelines. The NLA recommendations for apheresis are listed in Table 5. Recently published guidelines from the German Apheresis Working Group identify lower LDL-C thresholds for initiating apheresis. The German guidelines recommend that patients with FH should start lipid apheresis within 3 months of failure of diet and lipid-lowering therapies as follows: as primary prevention in patients with LDL-C levels higher than 160 mg/dL; as secondary prevention in patients with progressive cardiovascular events with LDL-C levels higher than 120 mg/dL to 130 mg/dL; and in patients with progressive CVD with Lp(a) levels higher than 60 mg/dL.

In the past, surgical approaches to the lowering of LDL-C have been used. Ileal bypass surgery has been shown to reduce LDL-C levels by approximately 40% and reduce cardiovascular events in patients with severely elevated LDL-C levels. Ileal bypass surgery is also associated with an 18% reduction in overall mortality over a 25-year follow-up period. Liver transplantation has been performed very rarely in selected patients with severe FH.

New Treatment Options for Familial Hypercholesterolemia

Over the last few years, clinical development has led to the emergence of a number of novel therapies for lowering LDL-C levels. Because of the lower LDL-C levels and reduced incidence of CHD observed in patients with a specific allele of PCSK9, a protease gene involved in the degradation of LDL-C, PCSK9 is another potential therapeutic target. AMG 145 is a monoclonal antibody to PCSK9 that was recently tested in a multicenter, double-blind, placebo-controlled, randomized, phase 2 trial in patients with HeFH unable to achieve an LDL-C level of less than 100 mg/dL despite therapy with statins with or without ezetimibe. Patients receiving AMG 145 had a significant reduction in mean LDL-C levels of up to 55% compared with a 1% increase in the placebo arm, with no significant toxicity (P < 0.001). REGN727/SAR236553 is a monoclonal antibody against PCSK9 that inhibits binding to the LDL receptor. REGN727 has been tested in a randomized, double-blind, placebo-controlled trial of patients with HeFH with LDL-C levels of 100 mg/dL or higher despite lipid-lowering therapy with diet therapy and a stable dose of statin with or without ezetimibe. Patients receiving REGN727 had a rapid reduction in LDL-C levels, with a mean decrease of 29% to 68% compared with a mean reduction of 11% with placebo.

Recently, mipomersen, a second-generation antisense oligonucleotide, was approved by the FDA as an adjunct to lipid-lowering medications and diet to reduce LDL-C, apo B, total cholesterol, and non-HDL-C in patients with HoFH. Apo B is important for the structure and receptor binding of lipoproteins, including LDL-C. Apo B is important for the structure and receptor binding of lipoproteins, including LDL-C. In a phase 3 trial of patients with HoFH randomly assigned to receive either mipomersen or placebo, patients receiving mipomersen had a mean reduction in LDL-C levels of 24.7% compared with 3.3% in patients receiving placebo (P = 0.0003). The most common adverse effect in patients receiving mipomersen was injection-site reactions.

The microsomal triglyceride transfer (MTP) inhibitor lomitapide is another agent recently approved by the FDA for the treatment of HoFH. The MTP protein is responsible for transferring triglycerides onto apo B, a necessary step for the production of LDL-C. In a clinical trial of lomitapide in patients with HoFH, a significant dose-dependent reduction in LDL-C...
levels was observed; however, adverse effects included increased aminotransferase levels and fat in the liver.92 Lomitapide has received FDA approval for use only in patients with HoFH, with the requirement of use through a restricted program called the JUXTAPID Risk Evaluation and Mitigation Strategy administered by the manufacturer.93

Effective novel therapies alone or in combination with statins, particularly agents that may provide additive reduction in LDL-C levels, may allow for elongated intervals between apheresis sessions—and perhaps may even completely eliminate the need for apheresis, as well as surgical treatment, while preventing early CVD and related comorbid conditions. Furthermore, novel therapies may provide clinicians with alternative or additional treatment options for lowering LDL-C or Lp(a) levels, particularly in patients who are intolerant of statins.

**Pediatric Considerations for the Management of Familial Hypercholesterolemia**

Specific recommendations exist for the management of children and adolescents with FH.94 Children aged 9 to 11 years should have a fasting lipid profile or a nonfasting non-HDL-C measurement as a universal screening for FH so that a diagnosis can be made before atherosclerosis develops. In the setting of a positive family history for FH, children should be screened at 2 years of age. FH should be suspected in children, adolescents, and young adults with LDL-C levels of 160 mg/dL or greater or with non-HDL-C levels of 190 mg/dL or greater.94 The NLA Expert Panel on Familial Hypercholesterolemia recommends initial treatment for pediatric patients with statin therapy beginning at the age of 8 years, although patients with HoFH may require treatment at an earlier age. The treatment goal for pediatric patients is a reduction in LDL-C levels of at least 50% or an LDL-C level of less than 130 mg/dL. Many pediatric patients with severe FH will not reach their target goals for LDL-C levels or be able to tolerate high doses of statins. The majority of pediatric patients with HoFH will require apheresis to achieve adequate control of LDL-C levels. Despite the use of high-dose statins or apheresis, some pediatric patients with severely elevated LDL-C levels may benefit from liver transplantation because the transplanted liver will have functional LDL receptors, thereby lowering LDL-C levels.94 Liver transplantation may be a curative therapy for children with HoFH, particularly those who have not developed cardiovascular complications.95 In 1 case series, 4 patients with HoFH and progressive coronary atherosclerotic disease received orthotopic liver transplantation after failure of medical treatment.96 Two patients were well 4, 9, and 11 years after transplantation, with 1 of these patients requiring no immunosuppression to prevent rejection for the last 6 years. The third patient died 2 years after transplantation due to a myocardial infarction.86 At the last follow-up, all 4 patients had normal serum cholesterol levels.86 However, this therapy should typically be avoided due to major complications such as operative complications, transplant rejection, infection, chronic hepatitis, and vascular and biliary complications, along with the need for lifelong immunosuppressive therapy.95,96

**Cost-Effectiveness of Therapy**

Both the acute and long-term costs associated with cardiovascular events are high.97,100 For example, in a managed care setting, the total first-year health care cost per patient after acute coronary syndrome was estimated at $22,529.97 In another managed care study, the total average annualized health care costs for the treatment of peripheral artery disease was $5,955.98 Limited cost-effectiveness data are available for the treatment of patients with FH, and additional research is needed (Table 6). In a model evaluating the effectiveness of high-dose statins in a non-FH population, long-term therapy with these agents was cost-effective for decreasing LDL-C levels and minimizing the risk for CVD.99 Cost-effectiveness models compare the incremental cost per quality-adjusted life-years to determine whether the intervention falls within a given threshold.40 Cost-effectiveness models have not been evaluated to determine whether treatment with high-dose statins in patients with FH is cost-effective. However, it is likely that the cost-effectiveness of high-dose statin treatment in patients with FH is similar to, if not greater than, that in individuals without FH, given the very high risk for CVD in patients with FH. Furthermore, the cost-effectiveness of statins will generally continue to decrease as the patents for these drugs expire.99 Indeed, over a longer-term period of treatment of more than 10 years, generic high-intensity statin therapy to lower LDL-C levels by 50% is more cost-effective than lower doses of statins in primary prevention in those without FH.101 As previously

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**TABLE 6**

<table>
<thead>
<tr>
<th>Research Needs for the Cost-Effectiveness of Screening and Treatment for Familial Hypercholesterolemia Based on Recommendations from the National Lipid Association</th>
</tr>
</thead>
<tbody>
<tr>
<td>Research Needs</td>
</tr>
<tr>
<td>Cost-effectiveness analysis of genetic screening</td>
</tr>
<tr>
<td>Cost-effectiveness analysis of various approaches to screening and treatment</td>
</tr>
<tr>
<td>Cascade screening</td>
</tr>
<tr>
<td>Low-density lipoprotein apheresis</td>
</tr>
<tr>
<td>Cost-effectiveness analysis of the benefits of aggressive therapy, including use of high-dose statins and new agents to treat patients to lower-than-usual target LDL-C levels</td>
</tr>
</tbody>
</table>

*Adapted from Goldberg AC, Hopkins PN, Toth PP, et al. Familial hypercholesterolemia.3*  
LDL-C = low-density lipoprotein cholesterol.
stated, the early identification and aggressive treatment of FH minimizes the risk for CVD.

Cascade screening is a cost-effective method for identifying patients with FH compared with primary prevention screening strategies. A lipid panel is sufficient for most cascade screening. In families at high risk for FH and with diagnostic uncertainty, DNA analysis may be performed. As described previously, NLA guidelines for the management of patients with FH do not recommend DNA testing for making a diagnosis. Once a mutation has been identified in a patient with FH, DNA analysis of the mutation and measurement of LDL-C levels in first-degree relatives have a specificity and sensitivity of almost 100% for the identification of relatives with FH. A cascade screening strategy that incorporates DNA diagnosis in the index case to guide testing of mutation-positive patients, but also LDL-C-based cascade screening in patients with either a clinically definite or a probable history of FH, has been shown to be more cost-effective than a strategy based on LDL-C levels alone. An analysis by Nherera et al. (2010) compared 4 cascade screening methods: (1) cholesterol only; (2) DNA analysis of the index patient and first-degree relatives and cascade screening only in the patient with the mutation; (3) DNA testing of the index case and cascade testing in all mutation-positive index cases and also relatives of patients with definite clinical evidence of FH with no mutation using LDL-C levels only to test for mutation; and (4) DNA testing of the index case and cascade testing in all mutation-positive index cases and also relatives of patients with definite or probable clinical evidence of FH with no mutation using LDL-C levels only to test for mutation. Screening method 4 was found to be the most cost-effective compared with current screening practices.

Although LDL-C apheresis is costly, this procedure decreases levels of LDL-C and other atherogenic particles, including Lp(a), with a reduction in the risk for CVD. However, numerous factors must be seriously considered when the benefits of apheresis are being weighed against its high cost, including the patient’s quality of life, disease severity, and the potential lack of access to the procedure due to the scarcity of facilities. Research into the cost-effectiveness of several areas in the screening and treatment of FH is still needed (Table 5). The NLA recommendations suggest that initial screening, initiation of therapy, and follow-up should be covered by health care insurance. According to the NLA, payers should also cover high-potency statins, combination therapies, LDL-C apheresis, and genetic testing.

Conclusions

In addition to the NLA recommendations for the management of dyslipidemias in patients with FH, the European Society of Cardiology and the European Atherosclerosis Society have recently published guidelines on the management of patients with dyslipidemias, including patients with HeFH or HoFH. Older guidelines on the management of patients with FH include NCEP ATP III.

FH is the most common genetic disease in the world but is also treatable. Early screening, early diagnosis, reduction of risk factors, and aggressive treatment are important for the optimal care of these patients. In particular, aggressive therapy can significantly lower the risk for premature CVD and prevent or delay the incidence of CVD-related events.

Effective treatment for FH requires an early clinical diagnosis; therefore, FH should be suspected and tested for in patients aged 20 years and older who have LDL-C levels of at least 190 mg/dL or non-HDL-C levels of at least 220 mg/dL; in patients younger than aged 20 years who have LDL-C levels of at least 160 mg/dL and non-HDL-C levels of at least 190 mg/dL; and in patients with these levels who have a family history of high cholesterol levels and heart disease in a first-degree relative.

In the managed care setting, clinicians need to be aware that patients with FH may need more aggressive treatment to lower LDL-C levels, including higher doses of statins, a more potent statin, or combination drug therapy, and to minimize the risk for CVD. Managed care organizations should optimize disease management by covering initial screening, treatment, and monitoring of patients for response, as well as more extensive coverage for payments related to drug therapy so as to include high-potency statins, combination therapies, and therapies for those patients who are intolerant of or unresponsive to statins.

Unfortunately, even high-dose statin therapy or combination therapy often does not reduce LDL-C and other atherogenic particles to adequate levels; consequently, patients with FH continue to be at an increased risk for CVD. This leaves a significant unmet need for additional therapies for patients with severe FH (patients with HeFH and LDL-C levels greater than 200 mg/dL after maximum tolerated lipid-lowering therapy who also have CAD, and patients with HoFH). Despite the often rigid formularies of managed care organizations, proper management of patients with FH requires their ability to receive currently approved therapies, such as higher doses of statins, combinations of other LDL-C–lowering therapies, and lipid apheresis. Patients will also need access to recently approved and emerging treatments, including apo B antisense inhibitors, MTP inhibitors, PCSK9 inhibitors, and other LDL-C–lowering agents. Mipomersen, an antisense inhibitor, has recently been granted approval by the FDA and, along with other novel agents, has been shown in initial clinical trials to effectively lower LDL-C levels when added to statin therapy. Some agents are in late-phase clinical trials. Some of these therapies have also shown the potential for lowering levels of Lp(a) and other atherogenic particles. These therapies may offer patients with severe FH additional options in addition to currently available therapies.
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Adherence to Antiretroviral Therapy in Managed Care Members in the United States: A Retrospective Claims Analysis

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BACKGROUND: Antiretroviral therapy (ART) extends life for patients with human immunodeficiency virus (HIV) infection. However, suboptimal adherence to ART may lead to disease progression and virologic failure. Earlier studies with combination ART demonstrated that as much as 90%-95% adherence was needed to prevent disease progression.

OBJECTIVE: To measure adherence to ART regimens in patients with HIV infection and analyze the clinical and demographic factors associated with ≥90% adherence.

METHODS: This study used retrospective claims data from a managed care organization (MCO). Members 18 years and older with an HIV diagnosis identified by medical claims were included in the cohort, and pharmacy claims were retrieved for these members. An ART regimen was established for each patient within a 120-day period after the most recent physician’s visit occurring between January 1, 2010, and August 31, 2010. For patients who were on an ART regimen recommended by the Department of Health and Human Services (DHHS) 2011 Guideline, adherence, as measured by medication possession ratio (MPR), was calculated based on pharmacy claims for 1 year after the end of the 120-day period. Logistic regression was used to examine the association between MPR ≥90% and age, sex, type of health plan, use of a single-tablet regimen (STR), inpatient and outpatient utilization, and direct health care costs.

RESULTS: Of the 4,547 adults with HIV diagnosis, 3,528 (77.6%) had received at least 1 ART. A DHHS-recommended ART regimen was identified in 2,377 patients with 1,136 (47.8%) receiving an STR. Mean MPR for patients on a DHHS-recommended ART regimen was 91.5 +/−14.0 with 73.1% of patients having achieved MPR ≥90%. In univariate analyses, sex, number of outpatient visits, cost of inpatient care, and use of STR were significantly associated with MPR ≥90%. In multivariate analysis, only male sex (P = 0.027), and use of an STR (P = 0.0009) were positively associated with MPR ≥90%. Patients on STR were 1.3 times more likely to achieve at least 90% adherence.

CONCLUSIONS: Adherence continues to be a challenge in patients with HIV. More than a quarter of patients who were on a DHHS-recommended ART regimen failed to achieve an accepted adherence MPR threshold of ≥90%. Modifiable prescribing practices may include using an STR, but other interventions to improve adherence are also needed.

SPONSORSHIP: This research was funded by Gilead Sciences, Inc., Foster City, CA.

Abstracts from Professional Poster Presentations at AMCP’s 25th Annual Meeting & Expo

Antiretroviral Persistence and Adherence and Total Health Care Expenditures in Medicaid-Insured HIV Patients Initiating Current Guideline-Preferred Compared with Nonpreferred First-Line Antiretroviral Therapy

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BACKGROUND: Current Department of Health and Human Services (DHHS) guidelines for the use of antiretroviral therapy (ART) in human immunodeficiency virus (HIV) recommend 4 specific “preferred” ART regimens for ART-naïve patients. In spite of these recommendations, real-world evidence suggests that providers sometimes prescribe nonpreferred ART. While the beneficial clinical aspects of preferred ART regimens are well described, the extent to which such benefits translate into improved ART persistence and adherence or lower health care expenditures is not.

OBJECTIVE: To compare ART persistence and adherence and total health care expenditures in Medicaid-insured HIV patients initiating current guideline-preferred or nonpreferred first-line ART.

METHODS: This is a retrospective study using Medicaid administrative health care claims from 15 states. Subjects were HIV patients aged 18 to 64 years who initiated first-line HIV-related ART between January 1, 2007, and September 30, 2011, with continuous enrollment for 6 months prior to and ≥3 months following ART initiation and no evidence of pregnancy or hepatitis B infection. Patients were classified as having initiated either a preferred ART regimen (preferred group) or nonpreferred ART regimen (nonpreferred group) based on current DHHS HIV treatment guidelines (March 2012). Outcomes were time to nonpersistence, adherence, defined as the number of days from ART initiation until a ≥30-day gap in initiated ART, introduction of a new ART medication, or censoring at disenrollment; adherence, defined as the proportion of days covered by ART medication during the period of persistence (dichotomized at ≥80% and ≥93%); and per-patient-per-month (PPPM) total health care expenditures measured during the period of persistence. Patients persistent for <30 days, who therefore had nearly perfect adherence during their period of persistence, were excluded from the adherence analyses. Time to nonpersistence, adherence ≥80% and ≥93%, and PPPM total health care expenditures were evaluated using multivariable Cox proportional hazards, logistic, and log-linear regressions, respectively. PPPM total expenditures were re-transformed to the dollar scale using 2 smearing factors, and expenditure-related inference was based on the recycled prediction method with 500 bootstrap repetitions.

RESULTS: Sample included 1,979 patients initiating a preferred regimen and 1,614 patients initiating a nonpreferred regimen, overall mean age 41 years, 48% female. Unadjusted incidence rates of nonpersistence per 10 years of treatment were 9 in the preferred group and 20 in the nonpreferred group. Unadjusted proportions of patients achieving ≥80% and ≥93% adherence were 87.2% and 50.8% in the preferred group and 81.9% and 43.1% in the nonpreferred group. Unadjusted mean (SD) PPPM total health care expenditures were $4,097 ($15,147) in the preferred group and $5,843 ($24,078) in the nonpreferred group. In
the multivariable analyses, the preferred group had significantly lower adjusted hazards of nonpersistence (hazard ratio = 0.48, 95% CI = 0.44-0.52) and significantly greater adjusted odds of adherence ≥80% (odds ratio [OR] = 1.38, 95% CI = 1.07-1.77) and adherence ≥95% (OR = 1.26, 95% CI = 1.05-1.51). PPPM total health care expenditures were numerically lower for the preferred group ($341, 95% CI = $388-$525) but the difference did not reach statistical significance.

**CONCLUSIONS:** Compared with patients initiating nonpreferred ART, those initiating preferred ART regimens had longer durations of ART persistence, were more likely to adhere to their ART, and had similar PPPM total health care expenditures.

**SPONSORSHIP:** This research was conducted by Bristol-Myers Squibb, Plainsboro, NJ, without external funding.

**Application of a Refill Reminder Program Aimed at Increasing Part D Plan Rating Medication Adherence Measures**


**BACKGROUND:** Literature reviews of medication adherence interventions specify reminding patients of refills as one of the most effective methods of increasing medication adherence to maintenance medications. A member-based refill reminder program to address gaps in therapy for at-risk members was implemented for a health plan with poor ratings to the 3 adherence-based Centers for Medicare and Medicaid (CMS) Part D Patient Safety measures. Program components included a pill box delivery to all members plus letters and phone calls to targeted members.

**OBJECTIVE:** To (a) implement a refill reminder program aimed at increasing member adherence and (b) to assess the influence of the program to a Medicare Advantage prescription drug plan's (case group) overall long-term adherence patterns and rates.

**METHODS:** Daily scans and analysis of a pharmacy claims database identified members late in refilling 3 classes of maintenance medications. Oral Diabetes (ODM), anti-hypertension (HTN), and cholesterol (CHOL). Letters in English and Spanish were prepared and sent daily to members late in refilling target medications by 7 days. Targeted members were monitored for refill status, and those not refilling within 7 days of first letter were sent a second refill reminder letter. Outbound telephone calls were made by care coordinators to those members who 7 days after the second letter reminder still had not refilled their prescriptions. Member and overall health plan adherence rates were measured pre- and post-intervention using proportion of days covered (PDC). Changes in adherence and number of members reaching adherence threshold (PDC ≥ 80%) were compared with another Medicare Advantage prescription drug plan (control group) with similar demographic characteristics not participating in the refill reminder program. Logistic regression was used to assess likelihood of reaching adherence post-intervention across groups while adjusting for baseline adherence rates.

**RESULTS:** A total 40,014 letters, at an average of 1,482 letters per week, were sent in the first 6 months post-implementation. Percentage of members refilling medication after the first and second letter was 14.9% and 21.3%, respectively. Adherence rates for the participating health plan increased 2.0%, 3.5%, and 4.0% from baseline for ODM, HTN, and CHOL, respectively. For all adherence-based CMS Part D Star Rating Measures, members in the case group were more likely to be adherent in the post-period than members in the control group: ODM (odds ratio [OR] = 1.407, 95% CI = 0.945-2.094), HTN (OR = 1.688, 95% CI = 1.318-2.163), CHOL: (OR = 1.570, 95% CI = 1.236-1.995).

**CONCLUSIONS:** In this Medicare population, members benefited from a repetitive refill reminder program to improve adherence to targeted maintenance medications. Refill reminders may contribute to development of clinical programs intended to improve a health plan's adherence-based Part D plan ratings.

**SPONSORSHIP:** This research was conducted by MedImpact Healthcare Systems, Inc., San Diego, CA, without external funding.

**Assessment of Prescription Utilization Patterns with the Shifts of Medicaid FFS to Managed Care in New York, Kentucky, Ohio, and New Jersey**

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**BACKGROUND:** With the Affordable Care Act provisions to expand Medicaid eligibility and the DRE Act to extend the rebate program to managed Medicaid enrollees, states are incentivized to shift programs from fee-for-service (FFS) to managed Medicaid plans (MMC) and to carve-in pharmacy benefits. Kentucky shifted patients into MMC in November 2011, Ohio carved-in pharmacy benefits to MMC in October 2011; New York shifted patients and all pharmacy benefits into MMC in October 2011; and New Jersey shifted patients and carved-in all pharmacy benefits to MMC in June 2011.

**OBJECTIVE:** To evaluate the impact on patients when shifted to MMC and to determine if the MMC plans manage prescription benefits differently than FFS by trending the average prescription fills and identifying changes in product mix among patients in New York, New Jersey, Ohio, and Kentucky across 3 therapy areas: diabetes, respiratory, and antipsychotics.

**METHODS:** This retrospective analysis utilized the IMS longitudinal patient data for January 2010 to June 2012. Patients were selected if they filled a prescription for a diabetes, respiratory, or antipsychotic drug that was billed to payers as Medicaid FFS or MMC. Patients with Medicare Part D prescriptions were excluded, and the remaining sample was divided into 11 cohorts based on the timing of prescription fills and the timing of the respective state policy change. This study describes patients in FFS during the entire study period (FFSx) and patients in FFS shifting to MMC (MMCx).

**RESULTS:** A total of 343,152 patients were analyzed. The table describes the state and therapy level changes in prescriptions per patient and percentage of brand utilization. MMCX patients had a 0% change in average prescriptions per patient. MMCX patients initiating therapy (12-month look back) in the post-period were less likely to be started on a branded product across states and therapy areas (62.8% MMCX compared with 55.9% FFSx). In the antipsychotics market, MMCX patients showed a 24.5% decline in brand utilization, compared with an 11.5% decline in FFSX patients among all states. Kentucky and New York showed the largest decrease in brand utilization among diabetes MMCX patients (Kentucky: -3.2%, New York: -7.8%). MMCX patients in New York and Ohio showed increases (New York: 5.3%, Ohio: 1.1%) in diabetic prescriptions per patient, whereas the FFSX diabetes cohorts had declines during the same time period (New York: -1.2%, Ohio: -3.8%). When examining the specific drugs that were filled among the New York diabetic MMCX cohort, a 13.5% increase was seen in use of metformin.

**CONCLUSIONS:** Each state showed different trends across therapy areas, demonstrating varied management tactics of the prescription benefit. Overall, MMC plans were able to provide access to the pharmacy benefit such that there was no disruption for patients when switched. Additionally, MMC plans have a more aggressive approach to brand utilization management when compared with FFS. For example, MMC plans were quicker in reacting to the patent loss of Seroquel in March 2013.
State and Therapy Area Results

<table>
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<tr>
<th>Average Prescription Per Patient</th>
<th>Percentage of Brand Utilization</th>
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<tr>
<td></td>
<td>Pre-Policy Shift</td>
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FFSx = patients in fee for service during the entire study period; MMCx = patients in fee for service shifting to managed Medicaid plans.

2012. It remains to be determined if the MMC cohorts that saw an increase in overall prescriptions were due to disease and case management programs that promote compliance and adherence.

SPONSORSHIP: This research was conducted by IMS Health Incorporated and IMS Institute, Parsippany, NJ, without external funding.

Association Between Adherence to Generic Statin Therapy and Outcomes: Total Cost of Care and Medical Events over 2 Years

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BACKGROUND: Previous research has found higher statin adherence associated with lower medical events but with higher total costs of care (TCC) due in part to brand statin costs. With the introduction of multiple generic statins, it is possible that members adherent to generic statins may have lower TCC. Minimal data is available quantifying outcome and cost differences in members adherent and nonadherent to generic statin medications.

OBJECTIVE: To examine the association between medication adherence and all-cause hospitalization or emergency room (ER) visits and compare TCC, medical costs, and pharmacy costs among individuals adherent and nonadherent to their generic statin therapies.

<table>
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<th>TABLE</th>
<th>Association of 2-Year Costs of Care and Medical Events with Generic Statin Adherence</th>
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<td>2-Year Outcomes Assessment</td>
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<td>Unadjusted all-cause hospitalization/ER visit</td>
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<td>All medical costs, $ (SD)</td>
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<td>All pharmacy costs, $ (SD)</td>
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<td>Total cost of care (medical and pharmacy), $ (SD)</td>
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*Hospitalization/ER visit rate compared by log-rank test and costs compared by GLM.

All medical costs are allowed amounts (plan and member paid) from all facility and professional claims including office visits, hospitalizations, procedures, laboratory testing, and ancillary. Medical costs plus pharmacy costs do not sum to total cost of care due to multivariate modeling using GLM with gamma log link. 

ER = emergency room; GLM = generalized linear model; PDC = proportion of days covered; SD = standard deviation.
METHODS: Retrospective pharmacy and medical claims data from a 1.2 million member commercial plan was used to identify members continuously enrolled from 2007 through 2010. Each member’s first 2008 medical encounter was defined as the index date. Members were required to have either two separate hypercholesterolemia (HC) office visits or an HC-related hospitalization in 2008 and have a statin supply on index date or a high risk condition diagnosis in the prior year. High risk conditions were defined as diabetes mellitus (DM), coronary artery disease (CAD), embolic stroke, or peripheral vascular disease (PVD). All members were followed for 2 years after their index dates and were required to have a >80% generic statin claim fill rate. In the 2-year follow-up, all statin claims were assessed to identify members as adherent (proportion of days covered [PDC] ≥80%) or nonadherent (PDC <80%). All medical and pharmacy claim total allowed amounts were summed to determine TCC. The Kaplan-Meier method was used for hospitalization/ER rate calculation, and association with adherence was analyzed using a Cox proportional hazard regression model with adjustment for age, gender, zip code-derived income, Charlson comorbidity score, existence of baseline depression or bipolar disorder, DM, CAD, PVD, or embolic stroke. Cost analyses were performed using the generalized linear model with gamma log link and adjusted for the same covariates.

RESULTS: Of the 21,910 members meeting all inclusion criteria, 10,126 (46.2%) were adherent, and 11,784 (53.8%) were nonadherent during the 2-year follow-up. The adherent group had a significantly lower hospitalization/ER visit rate (hazard ratio of 0.87, 95% CI, 0.82 to 0.92). Multivariate cost modeling found individuals in the adherent group had significantly lower medical costs ($1,022), higher pharmacy costs ($937), and lower TCC ($161).

CONCLUSIONS: In this 2-year study, individuals adherent to generic statin medication had an associated unadjusted 2.6 percentage point lower hospitalization/ER visit rate, which remained significantly lower in the multivariate Cox model. The significantly lower medical costs offset the higher pharmacy costs resulting in significantly lower TCC.

SPONSORSHIP: This research was conducted by Prime Therapeutics LLC, Eagan, MN, without external funding.

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**Budget Impact of the Introduction of a Low Dose Levonorgestrel-Intrauterine System from a U.S. Third-Party Payer Perspective**

**Kim RS,* Law A, McCoy MA, Ferrufino C, Hawes C, Poscik JP, Trussell J, Filomenko A. Bayer Healthcare Pharmaceuticals, 6 West Belt, Wayne, NJ 07470; ruth.kim@bayer.com, 973.487.5950**

**BACKGROUND:** Contraceptives vary by effectiveness, duration of effect, and the total costs related to the method used and unintended pregnancies (UP). Health care payers and women incur higher initial costs for long-acting reversible contraceptives, such as intrauterine contraceptives and implants, than for short-acting reversible contraceptives, such as oral contraceptives (OC). When making coverage decisions for contraceptives, health care payers should take into consideration both product- and pregnancy-related costs over the entire time of contraceptive use.

**OBJECTIVE:** To estimate the impact on the cost to a U.S. health care plan over 3 years when switching women from OCs to a low dose levonorgestrel-intrauterine system (LNG-IUS-12).

**METHODS:** A budget impact model was designed to estimate the cost before and after the availability of LNG-IUS-12, over a 3-year time horizon, among females 15–44 years at risk of UP, covered by a health plan. U.S. Census and National Survey of Family Growth data were used to determine the number of women aged 15–44 currently using or requiring contraception. Pregnancy outcomes (i.e., live births, induced and spontaneous abortion, ectopic pregnancy), risk of UP, discontinuation rates, and typical failure rates were estimated using published literature. It was assumed that LNG-IUS-12 garnered 0.5% of the contraceptive market in the first year, an additional 0.3% in the second year, and 0.2% in the third year, resulting in 1% of the contraceptive market at year 3, with LNG-IUS-12 taking direct market share from branded and generic OCs. The model incorporated costs for contraceptives, related physician visits, and pregnancy outcomes from method failures. Pharmacy costs were derived from Wolters Kluwer Health Medispan Master Drug Database; medical care costs were gathered from Medicare Reimbursement Rate for physicians; and the pregnancy costs were obtained from the Health Care Utilization Project. Model outputs were reported as cost per plan, per member, per patient, or per member per month (PMPM), as well as the number of UP. All costs accrued in years 2 and 3 were discounted at 3%. A scenario analysis assessed the impact of potential first-year discontinuation rates for LNG-IUS-12, allowing for a 20% switch from LNG-IUS-12 back to OC.

**RESULTS:** In a hypothetical cohort of 1 million plan members, the base case model, with no allowance for discontinuation, estimated a reduction in total costs of $516,166, in PMPM costs of $0.04, and in UP 153. When first-year discontinuation of LNG-IUS-12 was considered, the model estimated a decrease in total costs of $381,032, in PMPM costs of $0.03, and in UP of 134. These results were based on an estimated LNG-IUS-12 uptake of 1% of the total contraceptive market taken from OC users over a 3-year time horizon in women at risk for pregnancy.

**CONCLUSIONS:** Switching contraceptive users from OC to LNG-IUS-12 in a U.S. health care plan may result in less UP and an overall cost savings to the plan.

**SPONSORSHIP:** This research was conducted by IMS Health Incorporated, Parsippany, NJ, and Bayer Healthcare Pharmaceuticals, Wayne, NJ, without external funding.

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**Burden of Secondary Cardiovascular Disease in Commercial and Medicare Patients: A Managed Care Perspective**

**Carlton R, Clark R, Regan TS.* Xcenda, 4114 Woodlands Pkwy., Palm Harbor, FL 34685; Tim.Regan@xcenda.com, 727.771.4129**

**BACKGROUND:** The overall cost of secondary cardiovascular events in patients with a history of coronary heart disease (CHD), transient ischemic attack (TIA), or ischemic stroke represents a significant financial burden on managed care. Despite the American College of Cardiology (ACC)/American Heart Association (AHA) guideline recommendations to start aspirin therapy and continue indefinitely in all patients unless contraindicated, aspirin remains underutilized.
OBJECTIVE: To characterize the financial burden of secondary cardiovascular disease and its long-term complications in patients at risk for a secondary cardiovascular event.

METHODS: An economic model yielding the annual secondary cardiovascular disease cost burden was constructed using literature-based population, medication discontinuation/nonadherence, and cardiovascular event incidence data. Secondary cardiovascular disease patients were allocated to treatment either with aspirin, aspirin plus proton-pump inhibitor (PPI), or no aspirin. Secondary events were calculated based on annual recurrence rates adjusted for treatment discontinuation/nonadherence. The treatment cohort cost per member and total cost, along with the overall annual secondary cardiovascular disease expense to the plan, were determined based on AWP/MAC drug pricing and published discharge data for cardiovascular and gastrointestinal events.

RESULTS: A commercial plan with 1 million lives had an estimated 68,276 members who were considered to have secondary cardiovascular disease (26,753 who had experienced a stroke or TIA; 41,523 who had CHD). A Medicare population with 1 million lives had an estimated 295,711 members who have had secondary cardiovascular disease (124,451 stroke or TIA members, 171,260 CHD members). Of those members with secondary cardiovascular disease, 14.8% did not take any aspirin therapy, while 70.7% took aspirin (25.6% used aspirin alone, and 45.1% used aspirin + PPI). The remaining 14.5% of patients on an antplatelet other than aspirin with or without an anticoagulant were not the focus of this analysis and were excluded. The cost per commercial plan member per year for those in the aspirin cohort was $852; aspirin + PPI was $940, yielding an overall cardiovascular disease expense of $47.4 million to the plan.

The Medicare population was more expensive at an overall secondary cardiovascular disease expense of $202.8 million, or $863, $718, and $953 per member per year for the aspirin, aspirin + PPI, and no aspirin cohorts, respectively.

CONCLUSIONS: Prevention of secondary cardiovascular events with aspirin + PPI compared with aspirin alone was associated with a net per-patient per-year cost decrease of $103 and $145 and a potential overall cost decrease of $1.8 million and $11.0 million for a commercial and Medicare plan, respectively.

SPONSORSHIP: This research was funded by Pozen Inc., Chapel Hill, NC.

Comparable Cost Effectiveness of Subcutaneous Abatacept and Adalimumab in the Treatment of Patients with Rheumatoid Arthritis

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BACKGROUND: Several different classes of biologic agents are currently approved to treat adult patients with rheumatoid arthritis (RA) who responded inadequately to methotrexate (MTX). While numerous cost analyses for biologics have been performed, to date no study has compared the cost-effectiveness of biologics using data from a head-to-head trial of these agents. Here, we report the results of a comparative cost-effectiveness analysis from AMPLE (Abatacept Versus Adalimumab Comparison in Biologic Naive RA Subjects with Background Methotrexate), the first head-to-head trial of biologics in RA patients with an inadequate response to MTX.

OBJECTIVE: To compare the cost-effectiveness of subcutaneous (SC) abatacept versus subcutaneous adalimumab using efficacy endpoints from the AMPLE trial.

METHODS: AMPLE is a noninferiority trial comparing the efficacy of SC abatacept versus adalimumab in adult men and women with RA for ≤ 5 years and moderate to high disease activity as defined by DAS28-CRP (≥ 3.2) at screening, despite treatment with background methotrexate of at least 15 mg per week. A cost-effectiveness analysis was conducted to determine the cost per patient achieving a number of clinical and patient-reported (PRO) outcomes over 12 months. Twelve-month efficacy data including American College of Rheumatology (ACR) responses (ACR20, ACR50, and ACR70), remission (DAS28<2.6), physical function (defined as an improvement in Health Assessment Questionnaire [HAQ]-Disability Index score of ≥ 0.3 units), and activity limitation (captured using the Activity Limitation Questionnaire, which assesses the time over the previous 30 days that a patient had limitations in performing work or nonwork activities) were used for this analysis. The annual

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<th>Cost Efficacy Ratio for ACR Responses in the AMPLE Trial</th>
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<td></td>
<td>ACR20</td>
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<td></td>
<td>3 Months ($)</td>
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<tr>
<td>SC abatacept + MTX</td>
<td>11,398</td>
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<tr>
<td>[10,474-12,523]</td>
<td>[19,242-22,534]</td>
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<tr>
<td>Adalimumab + MTX</td>
<td>9,965</td>
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<td>[9,200-10,870]</td>
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ACR = American College of Rheumatology; AMPLE = Abatacept Versus Adalimumab Comparison in Biologic Naive RA Subjects with Background Methotrexate; MTX = methotrexate; SC = subcutaneous.
cost of therapy of SC abatacept (125 mg weekly) and adalimumab (40 mg biweekly) was computed based on the wholesale acquisition costs per unit dose multiplied by frequency of administration per dosing. Cost of MTX was not included in the calculation because it was assumed to be the same for both treatments.

RESULTS: At the end of 1 year, the cost-efficacy ratio between SC abatacept and adalimumab for all ACR response rates was consistently comparable over time (table). The mean cost per remission (95% CI) was comparable between SC abatacept ($63,282 [$55,807-$73,263]) and adalimumab ($59,458 [$52,010-$69,203]). The cost per HAQ response was comparable between the two groups ($45,366 [$41,643-$49,820] and $43,707 [$39,923-$48,188] for SC abatacept and adalimumab, respectively); cost per day gained without activity limitation was also similar ($323 [$287-$369] and $332 [$291-$387], respectively).

CONCLUSIONS: The cost-effectiveness of SC abatacept and adalimumab in adult RA patients with an inadequate response to MTX was comparable, based on measures of clinical efficacy and patient-reported outcomes.

SPONSORSHIP: This research was conducted by Bristol-Myers Squibb, Princeton, NJ, without external funding.

Comparative Effectiveness of First-Line Subcutaneously Versus Intravenously Administered Biologics for Rheumatoid Arthritis Using a Validated Claims Data-Based Algorithm in a Large U.S. Commercial Health Plan

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BACKGROUND: There is an increasing interest in comparative effectiveness research, especially for high cost and increasingly utilized drugs such as biologic therapies for rheumatoid arthritis (RA). Although health insurance claims routinely contain information on medication use, outpatient encounters, hospital discharges and costs, and have been commonly used to evaluate safety questions, they do not typically include measures of medication effectiveness in RA that can serve to quantify clinical benefit. A claims-based algorithm to evaluate effectiveness of biologics for RA was developed and validated using administrative data from the Veterans Health Administration (VHA) linked to the VA RA registry (VARA). VARA includes key clinical measures of RA disease activity commonly used in clinical trials such as the Disease Activity Score in 28 Joints (DAS28). The DAS28 served as the gold standard to validate the effectiveness algorithm.

OBJECTIVE: To compare the effectiveness of commonly used subcutaneously (SC) (adalimumab, etanercept, golimumab) versus intravenously (IV) administered (abatacept and infliximab) biologics approved for first-line treatment of moderate to severe RA among patients in a large national U.S. health plan using the claims-based algorithm.

METHODS: This retrospective cohort study used commercial claims data from OptumInsight’s Life Science Research Database, which contains medical and pharmacy claims for more than 13.3 million individuals with both medical and pharmacy benefit coverage. Biologic naive adult patients with RA (714.0x; no claims for a biologic in the preceding 6 months) continuously enrolled in the same health plan for at least 18 months, and who initiated treatment with either subcutaneously or intravenously administered biologics approved for RA were included. Patients with a diagnosis for plaque psoriasis, psoriatic arthritis, ankylosing spondylitis, juvenile idiopathic arthritis, Crohn’s disease, ulcerative colitis, non-Hodgkin’s lymphoma, and chronic lymphocytic leukemia were excluded. The algorithm used the following criteria to determine lack of effectiveness: low adherence to medication (medication possession ratio [MPR] < 80%) or receiving < expected number of infusions), increase in biologic dose or frequency, switching biologics, adding new nonbiologic diseases modifying anti-rheumatic drugs (e.g., leflunomide), new use of glucocorticoids or an increase in glucocorticoid dose, and more than 1 parenteral or intra-articular injection. No multivariate analyses to control for differences at baseline were conducted.

RESULTS: A total of 5,474 patients (4,406 SC, 1,068 IV) were included in the analysis. There was a similar percentage of females in both groups (77.7% SC vs. 78.4%) and a minor difference in mean age (48.4 years SC vs. 49.7 years IV; P < 0.001). More IV patients used methotrexate prior to baseline (60.4% SC vs. 65.1% IV, P = 0.004) and concomitantly (56.8% SC vs. 62.9% IV, P < 0.001). Overall, the algorithm classified SC-administered agents effective in a higher percentage of patients than IV agents (30.6% vs. 22.1%; P < 0.001).

CONCLUSIONS: Using a new validated claims-based algorithm to compare the effectiveness of first-line biologics approved for RA, SC agents were rated as effective in a higher percentage of patients than IV agents using the algorithm. Future work assessing costs of these agents could be used in conjunction with these results to assess the cost-effectiveness of these agents.

SPONSORSHIP: This research was funded by Immunex Corporation, a wholly owned subsidiary of Amgen Inc., and by Wyeth, which was acquired by Pfizer Inc. in October 2009, Thousand Oaks, CA.

Comparative Risks Associated with Off-Label Use of Individual Antipsychotic Drugs

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BACKGROUND: Despite a lack of evidence to support efficacy and a growing body of research showing antipsychotic use associated with serious adverse effects (e.g., Parkinson’s symptoms, cardiovascular problems, stroke, and higher risk of death), “off-label” prescribing of antipsychotic medications in the elderly remains high. FDA “black box” warnings on atypical (2005) and typical (2008) antipsychotics have had little impact on reducing use. The persistently high prescribing rates have resulted in a newly intensified federal focus on reducing antipsychotic use in the elderly. These initiatives mean that information about the comparative safety of individual drugs is of critical importance to providers and patients to help inform prescribing in cases where alternative therapies have not proven effective. Existing advisories do not distinguish between drugs and thus offer no guidance, and there is little extent research. One study (Huybrecht et al., BMJ, 2012) using 2001-2005 data found users of haloperidol had increased risk of mortality and users of quetiapine decreased risk, but no meaningful differences for other antipsychotic drugs. In the absence of clinical trials, large longitudinal health care databases provide a unique opportunity to examine comparative safety of individual drugs, providing new information that could be used to improve prescribing practices for the elderly managed care population.

OBJECTIVE: To evaluate the relative likelihood of adverse events associated with “off-label” use of individual antipsychotic medications in Medicare Advantage beneficiaries aged 65 years or older.

METHODS: This population-based cohort study analyzed patients in a large nationally representative administrative claims database. The sample consisted of Medicare Advantage patients aged 65 years or older who were treated with an antipsychotic medication between 2006 and 2011. Patients were identified by an index prescription fill for an antipsychotic drug. Patients were followed from 30 days up to 24 months after the index date to assess relative risk of death, hospitalization, emergency room visits, and stroke.
RESULTS: The study population included 69,927 patients prescribed an antipsychotic medication (female = 60.7%, mean age = 79.5 ± 6.8). The majority of antipsychotic prescribing was for “off-label” conditions (95.0%). Of those treated with antipsychotics, 22.6% had a diagnosis of dementia (without bipolar or schizophrenia), 17.1% anxiety disorder, and 12.7% depression; 3.7% and 1.5% were approved conditions bipolar disorder and schizophrenia, respectively. The top 5 medications were compared, including quetiapine, risperidone, haloperidol, olanzapine, and aripiprazole. Findings revealed significant differences in incidence of adverse outcomes for individual drugs; for example, incidence of death within 30 days of initiating treatment ranged from 9.4% of those prescribed haloperidol to 0.9% for aripiprazole.

CONCLUSIONS: “Off-label” use of antipsychotic medications in the elderly Medicare Advantage population remains high and results in significantly higher rates of adverse events. This study provides new information about the relative safety and incidence rates of most commonly used antipsychotics.

SPONSORSHIP: This research was conducted by Inovalon Inc., Bowie, MD, without external funding.

■■■ Comparing Health Care Resource Utilization and Costs in Medicaid Beneficiaries with Schizophrenia and Schizoaffective Disorders Before and After Initiation of Clozapine Monotherapy

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BACKGROUND: Treatment guidelines exist to guide the provision of quality care for patients with schizophrenia or schizoaffective disorders. Current guidelines support the utilization of clozapine monotherapy in patients with schizophrenia or schizoaffective disorders who have failed 2 prior antipsychotic treatments. The economic implications of the utilization of clozapine in Medicaid beneficiaries have not been widely discussed. Evidence of the trade-offs associated with clozapine use may be of interest to managed care pharmacists whose health plans increasingly serve Medicaid beneficiaries previously enrolled in Medicaid fee-for-services (FFS) plans.

OBJECTIVE: To compare health care costs and utilization in Medicaid patients with schizophrenia or schizoaffective disorders before and after initiation of clozapine monotherapy

METHODS: Data were from derived from the MarketScan Medicaid database. Inclusion criteria were (a) initiation of clozapine, with first such date identified as the index date; (b) receipt of at least 1 diagnosis of schizophrenia or schizoaffective disorder (ICD-9-CM of 295.xx) from 1 year prior to index date (pre-period) through 1 year post-index date (post-period); (c) continuous Medicaid enrollment between January 1, 2007, and January 1, 2009, for beneficiaries aged 18 through 64 years. Comparison of health care costs and utilization before and after initiation of clozapine therapy was assessed using paired t-tests and McNemar’s test for continuous and categorical variables, respectively. Each beneficiary served as their own case control. Pre/post outcomes of interest included changes in all-cause total direct medical payments as well as direct medical payments for treatment of all behavioral health therapy, expenditures for schizophrenia specific treatments, treatment for metabolic conditions such as myocardial infarction and diabetes, and those solely for the treatment of diabetic-related conditions. Health care resource utilization assessed variations in rates of inpatient admissions, emergency room (ER) utilization, and average length of inpatient stay.

RESULTS: 1,045 patients met the study inclusion/exclusion criteria for the pre/post assessment. The majority of the study cohort were white males with a mean [SD] age of 36.32 [12.5] years. Compared with the pre-period, direct medical payments for all-cause health care resource utilization decreased by 3.24% (P < 0.015) with reductions in inpatient expenditures offset by increases in outpatient payments. Direct medical payments for behavioral health treatments and schizophrenia specific treatments declined by 13.57% (P < 0.001) and 11.71% (P = 0.016), respectively. No statistically significant changes in direct medical payments for the treatment of metabolic disorders (P = 0.987) or diabetes (P = 0.912) were evident. No differences were observed in number of ER visits. Statistically significant reductions in all-cause hospitalizations (12.93%; P = 0.003), schizophrenia-related hospital stays (12.00%; P < 0.001), and hospitalizations for diabetes-related issues (38.33%; P = 0.038) were revealed. In addition, the average length of stay for any type of hospitalization declined from as little as 29.33% (P = 0.016) to as much as 98.56% (P < 0.001).

CONCLUSIONS: Initiation of clozapine monotherapy reduces hospitalizations in Medicaid patients with schizophrenia or schizoaffective disorders.

SPONSORSHIP: This research was conducted by Teva Pharmaceuticals, USA, Kansas City, MO, without external funding.

■■■ Comparison of Health Care Resource Usage and Costs Before and After Initiating Treatment with Long-Acting Injectable Antipsychotics Among Medicaid Insured Schizophrenia Patients

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BACKGROUND: Some studies on patients with schizophrenia have shown that schizophrenia relapses, hospitalizations, and inpatient care costs decline after patients begin treatment with long-acting injectable (LAI) antipsychotics; however, these results have contrasted with other studies. There is a need for further studies examining outcomes of patients with schizophrenia after beginning treatment with LAI antipsychotics to gain a more comprehensive understanding of their impact on disease management. In the United States, Medicaid insures the greatest population of patients with severe mental illness; however, patients with schizophrenia insured by Medicaid are less well studied than those insured commercially or by Medicare.

OBJECTIVE: To compare health care resource usage and costs before and after initiating LAI antipsychotics among Medicaid-insured schizophrenia patients.

METHODS: Schizophrenia patients ≥13 years of age initiating LAI antipsychotics were identified from the Thomson Reuters MarketScan Research Medicaid database between July 1, 2005, and June 30, 2010. Patients were required to have 6 months of continuous medical/precription drug coverage prior to (baseline) LAI initiation and during a variable follow-up period. Annualized health care resource usage and costs for the baseline and follow-up periods were determined and compared.

RESULTS: Among 5,694 eligible patients, 55% were male, and 45% were female with the majority of the population between the ages of 18 and 55 (86%). The study population had low general comorbidity as assessed by Charlson Comorbidity Index (CCI). In comparison to the baseline period, during the follow-up period (mean duration = 25.7 months) the mean number of hospitalizations per year, all cause (1.52 ± 2.41 vs. 0.70 ± 1.61; P < 0.001) and schizophrenia-related (1.21 ± 2.04 vs. 0.57 ± 1.41; P < 0.001) were reduced, as well as hospital lengths of stay (all cause: 14.77 ± 28.61 vs. 5.75 ± 16.26 days; P < 0.001; schizophrenia-related: 12.39 ± 25.86 vs. 4.67 ± 13.54 days; P < 0.001). As a result,
OBJECTIVE: To look at the proportion of nonmetastatic BC patients receiving T in an office clinic versus hospital outpatient setting and assess the impact of different sites of care on health care resource use (HRU) and costs.

METHODS: Adult women with BC (ICD-9-CM code 174.x) with 2 or more claims for a T infusion in a hospital outpatient or office clinic setting on or after 2008 were selected from the U.S.-based Humana database (2007-2012). Patients were required to be continuously eligible in their health care plans for ≥6 months prior to and ≥60 days following the first claims for a T infusion (index date). Patients with a diagnosis of secondary malignant neoplasm or who used T during the 6 months before the index date were excluded. T-treated patients were classified into 1 of the 2 cohorts: (1) hospital outpatient cohort, or (2) office clinic cohort. HRU and costs were measured over the period from the index date up to the end of continuous enrollment or up to 12 months after the index date, whichever occurred first. Differences in HRU were estimated using multivariate negative binomial regression models and reported as incidence rate ratios (IRRs). Monthly health care cost differences (2012 USD) were estimated using multivariate generalized linear or 2-part models. T-related HRU and costs were defined as medical services/costs associated with a medical claim for T administration.

RESULTS: A total of 861 patients met the inclusion criteria; 67% received T in an office clinic and 33% in a hospital outpatient setting. Baseline patient characteristics were relatively well balanced, except in terms of index years and insurance plan type: a higher proportion of patients in the hospital outpatient cohort had Medicare coverage (68.4% vs. 55.9%; P<0.001); Age at index date was also slightly different (mean: 64.3 vs. 62.1; P=0.019). Compared with the office clinic cohort, patients in the hospital outpatient cohort had a greater average total monthly cost (adjusted difference: $1,599; P<0.001) primarily driven by higher hospital outpatient and office clinic costs in the hospital outpatient cohort ($1,196; P<0.001). Similar findings were observed in terms of HRU where patients in the hospital outpatient cohort had a greater incidence of non–T-related visits (IRR=1.09; P=0.046) primarily driven by non–T-related hospital outpatient visits (IRR=2.01; P<0.001).

CONCLUSIONS: About one-third of patients received T in a hospital outpatient setting, and the majority had Medicare coverage. Patients treated in a hospital outpatient setting had higher costs and HRU compared with patients in the office clinic cohort. Further research is warranted to explore the impact of these findings on treatment duration and quality of care.

SPONSORSHIP: This research was funded by Genentech Inc., South San Francisco, CA.

Contrasting Adherence Measurement Methods and Considerations for Case-Mix Adjustment Under Star Rating Program

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BACKGROUND: Centers for Medicare & Medicaid Services (CMS) implemented a “star rating” program for Medicare Part D which assesses plan performance and rewards highest rated plans. Variations in calculating medication adherence may potentially yield different results. CMS uses proportion of days covered (PDC), while medication possession ratio (MPR) has also been used to measure adherence.

Abstracts from Professional Poster Presentations at AMCP’s 25th Annual Meeting & Expo

in comparison with before initiating LAI antipsychotics, annualized hospital payments (any cause: $16,249±$36,404 vs. $7,380±$21,087; P<0.001), schizophrenia-related: $13,388±$31,614 vs. $5,645±$15,767; P<0.001) were much lower (figure). Total outpatient medical service costs for any cause were not significantly different but, for schizophrenia, were slightly greater during the follow-up period ($3,461±$6,239 vs. $3,869±$6,425; P<0.001). Total health care costs (any cause: $28,774±$39,868 vs. $21,873±$27,188; P<0.001), including outpatient pharmacy costs, were significantly reduced after the initiation of LAI antipsychotics as compared with before they were tried.

CONCLUSIONS: Based on the results of this study, Medicaid-insured patients with schizophrenia who begin treatment with LAI antipsychotic therapy have better disease management afterward versus before, consequently, Medicaid incurs less cost for its care.

SPONSORSHIP: This research was funded by Otsuka America Pharmaceutical, Inc., Princeton, NJ.

Comparison of Health Care Resource Utilization and Costs Between Patients Who Received Trastuzumab in an Outpatient Hospital Versus Office Clinic Setting for the Treatment of Breast Cancer

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BACKGROUND: Patients receiving trastuzumab (T) for the treatment of nonmetastatic breast cancer (BC) may receive treatment in an office clinic or hospital outpatient setting. In recent years, an increase in patients receiving treatment in a hospital outpatient setting has been reported. This site of care shift could impact both costs and clinical outcomes.

FIGURE Differences in Hospital and Outpatient Medical Service Payments, Any Cause and Schizophrenia-Related for the Medicaid Study Population Before and After Initiation of LAI Antipsychotics

LAI = long-acting injectable.
OBJECTIVE: To assess and compare adherence for angiotensin-converting enzyme inhibitors (ACEIs)/angiotensin receptor blockers (ARBs) using PDC and MPR and identify factors associated with adherence that should be considered for CMS case-mix adjustment.

METHODS: This was a retrospective claims database analysis that used pharmacy claims and enrollment data for Part D beneficiaries. PDC and MPR for ACEIs and ARBs were calculated based on specifications from CMS and the Utilization Review Accreditation Commission (v1 for 2012 reporting). Descriptive analysis included reporting requirements and additional patient-level detail. Multivariate logistic regression analysis was used to identify factors associated with adherence. Case-mix-adjusted adherence was estimated using the predicted odds ratio (OR) for achieving PDC ≥80% and impact on plan rating was estimated based on the proportion of patients predicted to be adherent.

RESULTS: 134,901 patients were included in the PDC analysis. Mean PDC was 88.8%. The MPR analysis included 62,017 and 25,169 patients for ACEIs and ARBs, respectively. Mean MPR was 92% for both ACEI and ARB populations. Positive influencers of adherence were the following: female gender (OR = 1.12; P < 0.0001), total baseline pharmacy cost $150–$999 (OR = 1.24; P < 0.0001) and ≥$1,000 (OR = 1.59; P < 0.0001) versus $0–$149, ≥1 claim for ACEI/ARB with days’ supply ≥90 (OR = 2.26; P < 0.0001), hypertension (OR = 2.52; P < 0.0001), and hyperlipidemia (OR = 1.09; P < 0.0001). Some negative influencers included diabetes (OR = 0.91; P < 0.0001), anxiety/tension (OR = 0.90; P = 0.0001), coronary/peripheral vascular disease (OR = 0.896; P < 0.0001), and depression (OR = 0.83; P < 0.0001). Using CMS’s threshold for a 5-star rating (≥77.9%), 55.2% of plans achieved a 5-star rating compared with a predicted 72.4% of plans, if using a case-mix-adjusted model. Percentage of agreement between predicted and actual values for the model was 65.5%.

CONCLUSIONS: This study found higher adherence values for MPR compared with PDC. Gender, higher burden of illness, select comorbidities, and 90-day fulfillment were found to influence ACEI/ARB adherence. Quality-based performance measures, as well as coupled payment reporting. Descriptive analysis included reporting requirements and additional patient-level detail. Multivariate logistic regression analysis was used to identify factors associated with adherence. Case-mix-adjusted adherence was estimated using the predicted odds ratio (OR) for achieving PDC ≥80% and impact on plan rating was estimated based on the proportion of patients predicted to be adherent.

SPONSORSHIP: This research was funded by Takeda Pharmaceuticals U.S.A., Inc., Deerfield, IL.

Cost Analysis of Certolizumab Pegol and Infliximab Therapy at 1 and 2 Years in Patients with Crohn’s Disease

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BACKGROUND: Crohn’s disease is a chronic inflammatory disease of the gastrointestinal tract for which there is currently no cure. Long-term complications of uncontrolled disease include stricture, fistulizing disease, and surgery. Anti-tumor necrosis factor-α (TNF) therapy is increasingly being used in patients with Crohn’s disease who have an inadequate response to conventional therapy. Treatment goals are to modify the disease course and prevent long-term complications. There are currently 3 anti-TNF agents approved for the treatment of moderate to severe Crohn’s disease in the United States. Of these, only certolizumab pegol (administered subcutaneously) and infliximab (administered intravenously) can be billed against a patient’s medical insurance benefit.

OBJECTIVE: To evaluate treatment costs at 1 and 2 years in patients with Crohn’s disease who are prescribed an anti-TNF agent administered subcutaneously (certolizumab pegol: prefilled syringe or lyophilized [PFS/LYO]) or intravenously (infliximab).

METHODS: OptumInsight’s Clinformatics Data Mart, a database of administrative health claims from a large national health insurer, was used for analysis. U.S. patients who had a diagnosis of Crohn’s disease were identified and received a prescription for an anti-TNF from April 2008-January 2012. Patients were eligible for inclusion in the analysis if they were aged 18 years or older, had not received anti-TNF therapy in the 6 months prior to first anti-TNF, and had 24 months pharmacy and medical continuous enrollment in the database. Costs were presented in 2 ways: medication acquisition costs (direct cost of biologic only) and Crohn’s disease-related costs (includes all Crohn’s disease-related medications and administration, visits, and procedures). This study reports costs for patients still receiving the initial anti-TNF therapy at 1 year and at 2 years.

RESULTS: Over 1 and 2 years, the average biologic and Crohn’s disease-related costs (including biologic costs) were lower among patients treated with certolizumab pegol than patients treated with infliximab (table).

CONCLUSIONS: This analysis of a U.S. claims database showed that over 1 and 2 years patients prescribed a subcutaneous anti-TNF (certolizumab pegol) had lower claims costs than patients prescribed an intravenous anti-TNF (infliximab). Limitations of this type of database analysis may include the inability to account for disease severity and patient demographics and the fact that the number of patients with available claims based on utilization patterns at 1 and 2 years was low.

SPONSORSHIP: This research was conducted by UCB Pharma, Smyrna, GA; Truven Health Analytics, Inc., Atlanta, GA (formerly the Healthcare Business of Thomson Reuters), and OptumInsight/UHC, Duluth, GA, without external funding.

Cost-Effectiveness of Fingolimod Versus Teriflunomide for the Treatment of Patients with Relapsing-Remitting Multiple Sclerosis (RRMS)

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BACKGROUND: Multiple sclerosis (MS) is a chronic condition often associated with high economic burden. Previously published economic analyses have shown the relative economic efficiency of existing self-injected disease-modifying therapies (DMTs). However, the recent approval of oral DMTs warrants an evaluation of these newer agents for the treatment of MS.

OBJECTIVE: To estimate the cost per relapse avoided of fingolimod versus teriflunomide from a U.S. commercial payer perspective.
METHODS: This Microsoft Excel-based model estimated the cost-effectiveness of fingolimod compared with teriflunomide, the only 2 FDA-approved oral treatments for relapse-remitting multiple sclerosis (RRMS). The analysis calculated the cost per relapse avoided for each of the products over 2 years (including drug acquisition costs using wholesale acquisition cost [WAC], direct costs of managing relapses, and monitoring costs) divided by the number of relapses avoided. Cost data were derived from published sources. The relative risk reductions (RRR) for each DMT were obtained from the respective placebo-controlled phase 3 clinical trials (FREEDOMS and TEMSO), and the average number of relapses over 2 years for an untreated patient was obtained from published estimates. Univariate sensitivity analysis was performed to test the robustness of the model.

RESULTS: Fingolimod was the more cost-effective DMT, with a 2-year cost per relapse avoided of $92,630 in comparison with $125,564 for teriflunomide. Univariate sensitivity analysis of the cost per relapse avoided for fingolimod showed the results were most sensitive to the drug acquisition cost of fingolimod and the average number of relapses in untreated patients; however, the rank-order of the results remained unaffected. In a scenario where drug acquisition costs were varied at different ranges, the WAC of fingolimod had to be increased by 40% for the cost per relapse avoided of fingolimod to be higher than teriflunomide.

CONCLUSIONS: Fingolimod has a lower cost per relapse avoided compared with teriflunomide. This cost-effectiveness was driven by its high efficacy in reducing the frequency of relapses in MS patients.

SPONSORSHIP: This research was conducted by CDMI, LLC, Newport, RI, without external funding.

Costs and Discontinuation Rates Among Protease Inhibitor-Treated Hepatitis C Virus Patients in a Regional Health Plan

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BACKGROUND: Two triple therapy (protease inhibitor, pegylated interferon alfa, and ribavirin) options have emerged for patients with hepatitis C virus (HCV) genotype 1 infection. Both options have been tested in clinical trials and are supported for use by the major HCV treatment guiding organization. Due to the complicated regimens, potential side effects, and costs of treatment, discontinuation rates are a concern for payers, providers, and patients.

OBJECTIVE: To identify discontinuation rates, costs of treatment, and costs of discontinuation and adherence rates for HCV-treated patients among a regional health plan.

METHODS: Using a large health plan pharmacy database (approximately 1.2 million lives), all continuously enrolled health plan patients initiated on telaprevir or boceprevir were identified between May 1, 2011, and July 31, 2012. Based on telaprevir and boceprevir minimum initiation and futility treatment algorithms, claims-based assumptions were developed to identify patients as discontinuing, completing, or actively on therapy. Baseline characteristics, course of treatment, discontinuation rates of therapy, and costs of therapy associated with completing and discontinuing therapy were analyzed using descriptive statistics with each respective treatment.

RESULTS: A total of 326 protease inhibitor (PI)-treated patients were identified for this analysis: mean age 53.0; average length of PI therapy 11.3 weeks. Of the 326 patients, 270 patients (82.8%) were treated with telaprevir with the following breakdown (n, %): active therapy (26, 9.6%), discontinued therapy (88, 32.6%), and completed therapy (156, 57.8%). The mean treatment costs (PI + pegylated interferon) associated with completion and discontinuation of telaprevir therapy are $69,625.95 and $29,377.17, respectively. 56 patients (17.2%) were treated with boceprevir in this health plan with the following breakdown (n, %): active therapy (12, 21.4%), discontinued therapy (11, 19.6%), and completed therapy (33, 58.9%). The mean treatment costs (PI + pegylated interferon) associated with completion and discontinuation of boceprevir therapy are $48,086.64 and $13,877.73, respectively. Adherence rates for telaprevir and boceprevir were 92.3% and 88.0%, respectively.

CONCLUSIONS: Among this regional health plan, adherence to therapy was similar between both HCV treatment regimens. Discontinuation rates for both PIs were high in this claims-based analysis. Costs of discontinuation and completion of therapy were significantly higher in telaprevir-treated patients. Due to the similar adherence rates seen, health plans should incorporate the costs of discontinuation and completion of therapy when developing decision-making models for utilization management in HCV treatment.

SPONSORSHIP: This research was conducted by CDMI, LLC, Newport, RI, without external funding.

Diminishing Rate of Return? Health Outcomes Associated with Initiation of Basal Insulin After 1, 2, or 3+ Oral Antidiabetic Drugs Among Managed Care Patients with Type 2 Diabetes

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BACKGROUND: Timely initiation of insulin may help patients with type 2 diabetes mellitus (T2DM) not maintaining adequate glycemic control using oral antidiabetic drugs (OADs). However, real-world health outcomes data are limited.

OBJECTIVE: To descriptively assess real-world health outcomes associated with basal insulin initiation among T2DM patients previously treated with 1, 2, or 3+ OADs in a managed care setting.

METHODS: Using data from a national managed care claim database (IMPACT), this observational study included adult T2DM patients who initiated a basal insulin between January 1, 2001, and December 31, 2011, had a continuous health plan enrollment for 6 months before (baseline) and 12 months after insulin initiation (follow-up), and had 1 or more OAD prescription, but no use of pramlintide, GLP-1 receptor agonist, or insulin during baseline. Patients were stratified by number of OADs used during baseline (1, 2, or 3+ OAD). One-year follow-up outcome measures were treatment persistence, hemoglobin A1c levels, health care utilization, and costs.

RESULTS: A total of 62,644 patients were included (1 OAD: 16,481 [26.3%]; 2 OAD: 25,336 [40.4%]; 3 or more OAD: 20,827 [32.2%]). Significant baseline differences existed between the 3 groups. Overall, when compared with 2 or 3+ OAD patients, 1 OAD patients were sicker (Charlson Comorbidity Index 1.02 vs. 0.81 vs. 0.62), had higher rates of macrovascular diseases (congestive heart failure, 12.0% vs. 9.7% vs. 7.2%; peripheral vascular disease, 6.8% vs. 6.3% vs. 5.3%; and cerebrovascular disease, 7.2% vs. 6.6% vs. 5.0%), yet lower rates of neuropathy (10.2% vs. 11.3% vs. 11.2%) and retinopathy (8.2% vs. 9.8% vs. 11.9%), higher rates of hospitalizations (28.2% vs. 21.7% vs. 15.4%), emergency room (ER) visits (32.8% vs. 27.5% vs. 21.3%), hypoglycemia (5.4% vs. 4.7% vs. 3.9%), and higher health care costs ($16,408 vs. $13,132 vs. $10,774, figure). Baseline A1c levels were similar across the 3 groups (9.21% vs. 3.9%), and higher health care costs ($16,408 vs. $13,132 vs. $10,774, figure). Baseline A1c levels were similar across the 3 groups (9.21% vs. 9.23% vs. 9.15%). At the end of the 1-year follow-up, despite the
Objective: To describe treatment patterns and characteristics of patients who initiated disease-modifying therapy (DMT) for MS and were followed for 2 years.

Methods: Data were derived from the MarketScan Commercial and Medicare Supplemental databases, which are retrospective claims databases representative of the U.S. managed care population. The study population included adult MS patients who initiated treatment with an interferon beta, GA, or natalizumab on or after January 1, 2007, had at least 30 months of continuous data (6 months before and 24 months after the treatment initiation [index date]), and had not used any MS therapy 6 months prior to the index date (baseline). Baseline demographics, concomitant medications, and comorbid conditions were analyzed in relation to treatment switching and discontinuation patterns.

Results: Data from 6,181 MS patients initiating therapy with a single DMT (index therapy) were evaluated (76.7% female; mean age 44.6 years). The majority of patients (75.9%) had seen a neurologist between their MS diagnosis and the index date. Chronic pain and high blood pressure were among the most common comorbid conditions. Patient characteristics were similar regardless of index therapy. A total of 5,735 patients (92.8%) initiated treatment with a platform therapy, and 446 patients (7.2%) initiated treatment with natalizumab. During the 2-year follow-up, 72.2% of patients on platform therapy and 77.1% of those on natalizumab remained on their index therapies; discontinuation rates were 8.7% and 9.0%, respectively. Compared with patients who remained on index therapy, those who discontinued were significantly older, whether they started on platform therapies (mean age 45.0 vs. 46.4 years [P=0.004]) or on natalizumab (mean age 45.0 vs. 49.3 years [P=0.013]). Patients who discontinued platform therapy were less likely to have seen a neurologist (70.4% vs. 76.2%; P=0.008), but not significantly higher baseline rates of antidepressant and muscle relaxant use compared with patients who remained on index platform therapy. Of 5,735 patients starting on a platform therapy, 1,095 (19.1%) switched therapies after a mean (SD) of 330.7 (203.8) days. Among these patients, 861 (78.6%) switched to another platform therapy, while 209 (19.1%) and 25 (2.3%) switched to natalizumab and fingolimod, respectively.

Note: All data are P < 0.0001 versus baseline or indicated otherwise.

*P = 0.007.

OAD = oral antidiabetic drug

Disease-Modifying Therapy in Patients with Multiple Sclerosis: Treatment Patterns over 2 Years

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Background: Patients with multiple sclerosis (MS) whose disease activity is inadequately controlled with a platform therapy (interferon beta or glatiramer acetate [GA]) may switch to another platform therapy or escalate therapy to natalizumab or fingolimod, which were approved in the United States in 2006 and 2010, respectively.
Patients who switched from a platform therapy to natalizumab had more baseline intravenous corticosteroid use than patients who switched between platform therapies (31.6% vs. 20.3%; P < 0.001). Of the 446 patients starting on natalizumab, 62 (13.9%) switched therapies after a mean (SD) of 400.9 (197.5) days; 61 patients switched to a platform therapy, and 1 patient switched to fingolimod.

**CONCLUSIONS:** Most patients remained on their initial DMTs during the first 2 years of treatment. Of the patients who switched, the majority switched to other platform therapies, even though they may benefit from treatment escalation.

**SPONSORSHIP:** This research was funded by Biogen Idec Inc., Cambridge, MA.

### Early Adherence with Disease-Modifying Drugs Predicts Future Adherence in Patients with Multiple Sclerosis

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To evaluate early DMD adherence as a predictor of future adherence outcomes in patients with MS.

**OBJECTIVE:** To evaluate early DMD adherence as a predictor of future adherence with DMDs have often focused on demographic characteristics, comorbidities, or previous consumption of health care resources. To our knowledge, no one has investigated how early adherence with DMDs is able to predict future adherence outcomes in patients with MS.

**METHODS:** Adult MS patients (≥18 and ≤65 years) who received outpatient self-injected DMDs between January 1, 2006, and May 31, 2010, were identified using claims data from a national U.S. managed care database. The date of the first DMD claim was the analysis index date. Patients were required to have continuous prescription coverage for 12 months before and 24 months after the index date. Multivariate regression was used to predict future adherence using the proportion of days covered (PDC) in the first 60 days of early adherence with no additional variables showed an r-squared of 20.6%. Using only the pre-period and demographic variables to predict adherence during the year post-index yielded an adjusted r-squared of 2.3%. Adding 60 days of early adherence data increased the r-squared to 22.4%. As the time period of early adherence was increased, the explained variance as measured by adjusted r-squared values increased from 21.6% to 53.5% when an entire year of DMD adherence was used. Addition of the covariates to the model increased the r-squared by 1% to 2%.

**CONCLUSIONS:** Predictive models that rely only on early adherence with DMDs were able to explain the variance in future adherence outcomes to a greater extent than models based solely on baseline characteristics. Early DMD adherence offers a new and simpler modeling approach to predict future adherence in patients with MS.

**SPONSORSHIP:** This research was conducted by EMD Serono, Inc., Rockland, MA, and Pfizer Inc., New York, NY, without external funding.

### Economic Burden of Irritable Bowel Syndrome with Constipation: A Retrospective Analysis of All-Cause Health Care Costs

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**BACKGROUND:** The prevalence of irritable bowel syndrome with constipation (IBS-C) is estimated to be between 1.3% and 5.7% in the United States. However, little is known about the total health care costs associated with IBS-C.

**OBJECTIVE:** To evaluate total annual all-cause health care costs of IBS-C in different health plan benefit designs and assess the incremental costs associated with IBS-C in a commercially insured population.

**METHODS:** Patients aged ≥18 years continuously enrolled in 2010 were identified using claims from the HealthCore Integrated Research Database, which consists of 14 geographically dispersed U.S. health care databases. The date of the first DMD claim was the analysis index date. Patients were required to have continuous prescription coverage for 12 months before and 24 months after the index date. Multivariate regression was used to predict future adherence using the proportion of days covered (PDC) in the first 60 days of early adherence with no additional variables showed an r-squared of 20.6%. Using only the pre-period and demographic variables to predict adherence during the year post-index yielded an adjusted r-squared of 2.3%. Adding 60 days of early adherence data increased the r-squared to 22.4%. As the time period of early adherence was increased, the explained variance as measured by adjusted r-squared values increased from 21.6% to 53.5% when an entire year of DMD adherence was used. Addition of the covariates to the model increased the r-squared by 1% to 2%.

**CONCLUSIONS:** Predictive models that rely only on early adherence with DMDs were able to explain the variance in future adherence outcomes to a greater extent than models based solely on baseline characteristics. Early DMD adherence offers a new and simpler modeling approach to predict future adherence in patients with MS.

**SPONSORSHIP:** This research was conducted by EMD Serono, Inc., Rockland, MA, and Pfizer Inc., New York, NY, without external funding.

### Predictive Models that Rely Only on Early Adherence

**RESULTS:** There were 4,606 patients who met the study criteria. The average age was 46.0 (SD 9.4) years, and 78.7% were female. Average PDC in the first 360 days post-index was 80.0% (SD 26.0). A total of 8.8% had at least one hospitalization, and depression/stress (22.8%) were common. Using only the first 60 days of early adherence with no additional variables showed an r-squared of 20.6%. Using only the pre-period and demographic variables to predict adherence during the year post-index yielded an adjusted r-squared of 2.3%. Adding 60 days of early adherence data increased the r-squared to 22.4%. As the time period of early adherence was increased, the explained variance as measured by adjusted r-squared values increased from 21.6% to 53.5% when an entire year of DMD adherence was used. Addition of the covariates to the model increased the r-squared by 1% to 2%.

**CONCLUSIONS:** Predictive models that rely only on early adherence with DMDs were able to explain the variance in future adherence outcomes to a greater extent than models based solely on baseline characteristics. Early DMD adherence offers a new and simpler modeling approach to predict future adherence in patients with MS.

**SPONSORSHIP:** This research was conducted by EMD Serono, Inc., Rockland, MA, and Pfizer Inc., New York, NY, without external funding.
plans representing 45 million members. IBS-C patients were defined as having ≥1 medical claim with an ICD-9-CM code for IBS (564.1x) and ≥2 medical claims with an ICD-9-CM code for constipation (564.0x) or ≥1 medical claim for constipation plus >1 pharmacy claim for a constipation-related prescription. Controls without IBS, constipation, abdominal pain, or bloating were randomly selected using 1:1 matching on age, gender, health plan region, and type of health plan benefit design. Patients with potentially confounding conditions (e.g., chronic diarrhea or drug-induced constipation) were excluded. Patients were categorized by health plan benefit design into noncapitated health maintenance organizations (HMO), preferred provider organizations (PPO), Medicare Advantage, and other benefit designs. Total all-cause health care costs consisted of pharmacy costs and costs of medical services, including inpatient visits, emergency room visits, physician office visits, and other outpatient services. Generalized linear models with bootstrapping were used to assess the incremental costs attributable to IBS-C adjusted for demographics and general gastrointestinal-related comorbidities.

RESULTS: Of 7,652 IBS-C patients and controls identified, 74.3% had a PPO design, 14.9% had a noncapitated HMO benefit design, 4.4% had Medicare Advantage, and 6.8% had a variety of other health plan benefit designs. Overall, the mean age (±SD) was 48 (±17) years, and 83.6% were female. IBS-C patients had consistently higher unadjusted total annual all-cause health care costs versus matched controls in the overall study population and among each of the health plan benefit designs (see figure). Higher unadjusted all-cause costs were primarily driven by medical costs regardless of health plan benefit design (81%-84% of total costs; figure). This finding remained consistent in the overall study population even after adjusting for demographic characteristics and comorbidities, with total incremental all-cause costs associated with IBS-C of $3,856 (P<0.001), and 79.2% of this difference driven by medical costs.

CONCLUSIONS: These findings highlight the significant economic burden of IBS-C in a commercially insured population, with a consistent burden observed across different types of health plan benefit designs. Medical services were the primary driver of incremental all-cause costs regardless of health plan benefit design.

SPONSORSHIP: This research was conducted by Forest Laboratories, Inc., Jersey City, NJ, and Ironwood Pharmaceuticals, Inc., Cambridge, MA.

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**Economic Burden of Pain in a National Health Insurance Plan**

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BACKGROUND: Pain is multifunctional; thus, it can be challenging to treat. The cost implications of pain-related health care resource utilization (HCRU) are substantial. Understanding the economic burden of pain HCRU will enable providers and payers to allocate resources more efficiently for improved management of different pain conditions.

OBJECTIVE: To track the annual HCRU (inpatient, outpatient, emergency room visits, and pain-related medications) associated with 36 chronic and 14 acute pain conditions and calculate the corresponding costs per member. These estimates were used to rank the economic burden of each condition in terms of expense to the plan.

METHODS: This retrospective study utilized enrollment, medical, and pharmacy claims data from Humana's fully insured commercial and Medicare membership. Study subjects were identified with a pain condition specified by an ICD-9-CM diagnosis in the primary diagnosis position on the medical claim during the index period (July 1, 2008–September 30, 2011). A second diagnosis ≥90 days from the first was required for chronic conditions, and no diagnosis of the index condition prior to the index date was required for acute conditions. HCRU and costs were tracked over a 365-day period subsequent to the index date. Additionally, all pain-related prescription medications were measured. HCRU and costs for the pain conditions were estimated per member and informed unadjusted estimates of annual costs from the plan's perspective for each specific pain condition. Conditions were ranked based on log-linear adjusted cost models. All analyses were stratified by membership in commercial or Medicare plans.

RESULTS: The impact of specific pain conditions varied by plan type. For commercial plans, 267,948 members were identified with a chronic or acute pain condition. The most expensive conditions were back pain (adjusted annual plan-wide costs were $119 million), osteoarthritis ($98 million), childbirth ($69 million), injuries ($61 million), and nonhip/nonspine fractures ($48 million). The most expensive pain-related conditions per commercial member were burns reclassified as chronic (adjusted cost per member $140,524), spinal cord injuries ($77,093), and repeated spine fractures ($25,931). For Medicare plans, 596,616 members were identified with a chronic or acute pain condition. The most expensive conditions to the plan were osteoarthritis ($327 million), back pain ($218 million), hip fractures ($117 million), injuries ($82 million), and nonhip/nonspine fractures ($67 million). The most expensive pain-related conditions per Medicare member were burns ($272,343), repeated hip fractures ($21,058), and acute hip fractures ($12,336).

CONCLUSIONS: Total pain-related expenses to the plan were higher for the Medicare population. Several of the most expensive pain conditions per member do not have a significant impact on total plan-wide costs, as overall prevalence is low. The economic burden of back pain and osteoarthritis was substantial in both plan populations, and hip fractures was substantial in the Medicare population. Further examination specific to how pain is managed in these high cost conditions will enable providers and payers to develop strategies to improve patient outcomes through appropriate pain management.

SPONSORSHIP: This research was funded by Humana Inc., Louisville, KY, and Pfizer Inc., New York, NY.

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**Establishment and Evaluation of a Pharmacist-Run Lipid Clinic Within a Managed Care Organization**

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BACKGROUND: Heart disease is one of the leading causes of death and disability in the United States, resulting in approximately 700,000 deaths per year. One of the most prevalent risk factors for heart disease-related deaths is dyslipidemia. This study attempts to analyze the impact of adding pharmacist care for lipid management in diabetes mellitus patients by creating a telephone-based lipid clinic within a managed care organization.

OBJECTIVE: To integrate with the organization's existing diabetic case management team to assist with reducing patients' low-density lipoprotein (LDL).

METHODS: A retrospective chart review was conducted on all patients enrolled in the pharmacist-run clinic who had appropriate follow-up laboratory data. Baseline LDL values were recorded and compared with values obtained at follow-up using a paired t-test. Pharmacist interventions, patient adherence, and the incidence of adverse drug reactions prior to and during clinic enrollment were also recorded.

RESULTS: Patients that were enrolled in the pharmacist-managed lipid clinic had a mean reduction in LDL of 17 mg/dL (P<0.0001). Data
regarding triglycerides, high-density lipoprotein, and total cholesterol was incomplete and could not be evaluated. During the study period, 290 pharmacist interventions were documented. The majority of interventions pertained to medication management/education, providing lifestyle education, and reminding patients to follow up with appropriate labs.

CONCLUSIONS: The pharmacist-managed clinic at Sharp Rees-Stealy Medical Center showed statistical significance in reducing diabetic patients’ LDL. The clinic also demonstrated that pharmacists provided patients with a substantial amount of education regarding medication, therapeutic lifestyle modifications, and appointment adherence.

SPONSORSHIP: This research was conducted by Sharp Rees-Stealy Medical Centers, El Cajon, CA, without external funding.

Evaluation of a Claims-Based Algorithm to Determine the Effectiveness of Biologics for Rheumatoid Arthritis Using Commercial Claims Data

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BACKGROUND: As more biologics are approved for moderate to severe rheumatoid arthritis (RA), there is an increasing interest in comparative effectiveness between agents. Health insurance claims have data from large numbers of patients and are commonly used to evaluate safety questions but do not typically contain information on commonly used clinical measures to quantify effectiveness (i.e., improvement in arthritis symptoms). A recently published algorithm was developed using Veterans Health Administration claims data and validated against the DAS28ESR data from the national VA RA registry to enable evaluation of the effectiveness of biologics for RA using only claims data.

OBJECTIVE: To confirm the utility of this claims-based effectiveness algorithm using a commercial claims data source.

METHODS: Data came from a previous comparative-effectiveness study using outpatient medical records from multiple U.S. institutions and private physician practices, linked to commercial claims data from OptumInsight, to evaluate the effectiveness of etanercept (ETN), adalimumab (ADA), and infliximab (INF) in commercially insured, biologic naive (no biologic use in the prior 6 months) adult RA patients persistent on their initial biologic for ≥1 year from 2006-2008. Two teams of 2 rheumatologists reviewed each medical record and categorized clinical response at approximately 1 year as follows: much better, better, no change, worse, or much worse. For this study, the biologic was considered not effective if the patient was rated as “no change,” “worse,” or “much worse.” Sensitivity, specificity, and negative predictive value could not be determined because patients who switched biologic agents or had low adherence were excluded from the original study sample. The biologic was considered not effective by the claims-based algorithm if any of the 6 previously published criteria was met: adherence to medication (medication possession ratio [MPR] <80% or receiving less than the expected number of infusions), increase in biologic dose or frequency, switching biologics, addition of new nonbiologic disease-modifying antirheumatic drugs, increase in glucocorticoid dose, and >1 parenteral or intra-articular injection. The positive predictive value (PPV) was calculated comparing the classification assigned by the algorithm to the rheumatologist rating from the previous study as the clinical gold standard. Different compliance thresholds (e.g., MPR ≥75% vs. ≥80% and lowering the required number of infusions for INF to expected -1 were evaluated as sensitivity analyses.

RESULTS: A total of 429 patients were available for study. The majority (76%) were female, mean age of 51 years. Overall, PPV of the effectiveness algorithm was similar in the main analysis (86.6%) and in the sensitivity analysis (86.5%). The PPV did not differ by biologic (P>0.2): INF (95%), ETN (86%), and ADA (85%). The PPV of each component of the algorithm was lower than that of the complete algorithm.

CONCLUSIONS: A previously published and validated claims-based algorithm to assess effectiveness of biologics for RA had high PPV in an independent dataset of commercially insured patients. This algorithm may be useful to compare the effectiveness of biologic agents for RA using health plan claims data in future studies.

SPONSORSHIP: This research was funded by Immunex Corporation, a wholly owned subsidiary of Amgen Inc., and by Wyeth, which was acquired by Pfizer Inc. in October 2009, Thousand Oaks, CA.
CONCLUSIONS: Beneficiaries in this Medicare-eligible population benefited from multiple points of contact to achieve increased adherence. A health plan's pharmacy and care management team can effectively utilize pharmacy and benefit management partners to offer novel methods to improve beneficiary and overall health plan medication adherence.

SPONSORSHIP: This research was conducted by MedImpact Healthcare Systems, Inc., San Diego, CA, without external funding.

Evaluation of an Interactive Voice Response Program to Influence Patient Behavior with Antihypertensives Use

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BACKGROUND: A brand-to-generic program for angiotensin receptor blockers (ARBs) using interactive voice response (IVR) technology as the communication channel was administered. The goal of the program was to increase member engagement while promoting cost-saving opportunities. Members filling a nonpreferred ARB (target drug) were identified on a weekly basis for IVR communication to switch to a preferred drug.

OBJECTIVE: To compare cost for ARB treatment for individuals who switched to preferred agent versus nonswitchers and describe the persistence of the preferred medication after a successful switch at 6 months post-intervention.

METHODS: A commercial health plan's members with at least 1 fill of a nonpreferred ARB from August 1, 2011, through October 31, 2011, were targeted. Members were identified once, but a member could receive up to 2 outbound call attempts. Successful conversion from target to preferred ARB, time to switch, days supply for target and preferred ARB fills, and costs for ARB treatment were assessed in the 6-month post-intervention period. The intervention date was defined as the date the IVR call was authenticated. Cumulative days supply for the target and preferred ARBs were used as proxies for persistence.

RESULTS: 1,054 members were authenticated through IVR, and 14.5% (n = 153) successfully switched to a preferred ARB. Among switchers, median time to switch was 59.0 days [SD = 69.6]. On average, switchers had 2.8 claims [SD = 2.2] for the target drug before switching and 3.4 claims [SD = 2.3] for the preferred drug during the 6-month period. For switchers, median copay for the target drug was $35.00 [SD = 29.96] versus $6.75 [SD = 5.81] for preferred drug, median plan paid amount for the target drug was $57.45 [SD = 33.62] versus $0 [SD = 2.99] for preferred ARB. Among nonswitchers (n = 901), median copay per target drug claim was $33.00 [SD = 29.01], and median plan paid amount per target drug claim was $63.68 [SD = 40.87]. On average, nonswitchers had 6.2 claims [SD = 3.1]. Cumulative 6-month ARB cost for both switchers and nonswitchers was $683,213, with plan paid amount of $421,247. For switchers, plan paid amount for ARBs was $28,006 versus $393,241 for nonswitchers. Based on the number of switchers (n = 153), the average ARB cost for a switcher was $183.05 versus $436.45 for nonswitchers (n = 901). Switchers' average cumulative days supplied was 90.4 days [SD = 68.6] and 151.3 days [SD = 79.3] for target and preferred drugs, respectively, versus 198.0 days [SD = 76.9] for nonswitchers.

CONCLUSIONS: The study found that using IVR technology to encourage member behavior change was effective in promoting the use of preferred ARBs and reducing drug costs for patients and payer, while achieving better persistence on ARB therapy.

SPONSORSHIP: This research was conducted by MedImpact Healthcare Systems, Inc., San Diego, CA, without external funding.

Evaluation of Increased Adherence and Cost Savings of an Employer Value-Based Benefits Program Targeting Generic Antihyperlipidemic and Antidiabetic Medications

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BACKGROUND: A major employer implemented a change to its employee health benefits program to allow beneficiaries with diabetes or high cholesterol to obtain specified generic antidiabetic or antihyperlipidemic medications at zero dollar copayment. To receive this benefit, plan beneficiaries were required to participate in a contracted vendor's case management and/or wellness program.

OBJECTIVE: To assess changes in medication adherence and expenditures for generic antidiabetic and antihyperlipidemic medications resulting from participation in a zero copay program.

METHODS: This was a retrospective pre/post comparison group study. The employer's de-identified prescription drug records were examined for this study from January 2009 through December 2011. Eligibility for program participation required participation in the vendor's case management or wellness program. Zero copay program participants and nonparticipants were matched on age, gender, comorbidity count, and baseline fill count via 1:1 propensity scoring, resulting in 218 antidiabetic only (AD) matched pairs, 798 antihyperlipidemic only (AH) matched pairs, 599 antidiabetic matched pairs who were users of both antidiabetic and antihyperlipidemic medications (ADAH), and 601 anti-hyperlipidemic matched pairs who were users of both medications. The proportion of days covered (PDC) metric was used to assess adherence to medication therapy.

RESULTS: In the AD, AH, and ADAH subgroups, zero copay users exhibited statistically higher absolute mean changes in PDC from the pre-period to the post-period when compared with the comparison group (15.5%, P < 0.001; 17.5%, P < 0.001; 3.9%, P = 0.005; and 6.7%, P < 0.001, respectively. This represented, on average, 40 additional days of medication possession by the zero copay users. The nonzero copay and zero copay groups exhibited different drug switching patterns from the pre- to post-period. Fewer nonzero copay patients switched from brand to generic drugs compared with zero copay patients. In the nonzero copay group, despite a decline of 3.4% in utilization, average cost per member per year (PMPM) rose by $35 (4.8%). In the zero copay groups, reductions in copays were associated with a slight increased utilization of 0.4%. However, average cost per utilizing member per year decreased by $18 (3.1%) in the zero copay group because of the shift from brand name to generic drugs. The difference between the cost increase in the nonzero copay group and the cost reduction in the zero copay groups was $53. The program saved $117,369 during the 12-month time frame or 8.1% of total allowed costs inclusive of employer and beneficiary portions of cost.

CONCLUSIONS: Plan sponsors are increasingly evaluating the use of Value-Based Benefit Design to change member behavior. This program used a reduction in cost-sharing to incent members to use more generic drugs and to enroll in a care management coaching program. When considering the introduction of such a design, plan sponsors are often concerned that the reduction in cost-sharing may increase the sponsor’s cost without inducing changes in behavior of the noncompliant members. Our study indicated that a plan sponsor can achieve the desired goals (increased drug adherence and generic drug penetration) without increasing the plan sponsor’s cost.

SPONSORSHIP: This research was conducted by Walgreen Co., Deerfield, IL, without external funding.
Evaluation of Natalizumab (Tysabri) Utilization and Costs for Utilization Management Opportunities

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BACKGROUND: Natalizumab (Tysabri) is a humanized monoclonal antibody that is FDA-approved for Crohn’s disease (CD) and relapsing forms of multiple sclerosis (MS). It is generally recommended for patients who have had an inadequate response, or are unable to tolerate, an alternative MS therapy. Fatal progressive multifocal leukoencephalopathy (PML) has occurred in patients who received natalizumab. Natalizumab is given as a 300 mg intravenous infusion every 4 weeks, and the 2012 wholesale acquisition cost (WAC) is $3,591. The WAC of natalizumab has increased almost 40% over the last 2 years.

OBJECTIVE: To evaluate natalizumab utilization patterns and to identify utilization management opportunities.

METHODS: Pharmacy and medical claims data from approximately 8.1 million commercially insured members were queried for 12 months from July 1, 2010, to June 30, 2011. The individual’s first natalizumab claim was defined as the index claim. Quarterly total paid natalizumab costs, unique utilizers, and claims trends were assessed. Natalizumab users’ diagnoses were identified from an evaluation of all medical claim ICD-9-CM codes during July 1, 2010, to June 30, 2011. A new natalizumab user was defined as not having had a natalizumab claim in the 6 months prior to the index claim. All claims among new users continuously enrolled for 6, 24, and 60 months prior to the index claim were assessed for evidence of an alternative MS drug.

RESULTS: Natalizumab utilization appeared stable at 754 (range 736 to 780) utilizing members per 8.1 million commercially insured lives per quarter during the 12 months of analysis (July 1, 2010, to June 30, 2011). Claims utilization was flat at 2,076 claims per quarter (range 2,019 to 2,138). Total 12-month natalizumab expenditures were $26,669,927 of which $26,407,773 (99.0%) was paid via the medical benefit. The natalizumab total paid per member per month (PMPM) increased from $0.24 in 2010 Q3 to $0.30 in 2011 Q2 consistent with the manufacturer price increases. All members had a medical claim with an ICD-9-CM diagnosis code for MS, and 5 (2.4%) also had medical claims for CD. In the 6-month follow-up, 50.7% of natalizumab new initiators did not have a history of an alternative MS agent claim. The percentage of members with no alternative MS agent decreased to 39.0% and 26.3% for 24- and 60-months follow-up, respectively (see table).

CONCLUSIONS: Management of the specialty MS drug natalizumab requires an integrated evaluation using both medical and pharmacy claims. The 25% natalizumab PMPM increase was largely due to manufacturer price increases. Health insurers can expect to face continued price increases despite flat utilization trends. Since 1 in 4 members newly initiating natalizumab did not have evidence of an alternative MS agent claim over 5 years, a medical policy or prior authorization encouraging a trial of an alternative MS agent before natalizumab may improve the quality of care by reducing the risk of natalizumab-induced life-threatening PML.

SPONSORSHIP: This research was conducted by Prime Therapeutics LLC, Eagan, MN, without external funding.

Evaluation of Pharmacist Knowledge and Attitude Toward Pharmacogenomics

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BACKGROUND: Pharmacogenomics is defined as the collection of genomic factors that influence an individual’s variability to drug response, including absorption, metabolism, distribution, excretion, and targeted enzyme-substrate activity. Pharmacogenomics has the potential to shift current guidelines in patient care practices. Personalized pharmacogenomics-targeted pharmaceuticals involve the use of drug companion tests and other genetic tests to increase drug efficacy while minimizing unwanted side effects by identifying biomarkers in patients early in the course of drug treatment. Pharmacists are experts in drug therapies and thus are the most logical health care professionals to bridge and integrate pharmacogenomics into drug therapy management.

OBJECTIVE: To develop and conduct a survey to assess pharmacists’ knowledge of approved oncology pharmacogenomic companion tests and attitude toward pharmacogenomic tests in general.

METHODS: An electronic survey was utilized to collect data on demographics, knowledge base, and attitudes toward pharmacogenomic tests and approved oncology companion tests on the market and distributed to pharmacists through state pharmacy organizations and alumni associations beginning in May 2012 and continuing through July 2012. The survey evaluated demographic data, attitudinal scales, a 12-item pharmacogenomic knowledge test, and policy/utilization data at their respective organizations. The study was approved by the Investigational Review Board of the University of Texas.

RESULTS: Analysis of 104 returned surveys was conducted. Of the pharmacists surveyed, 31% indicated that they work in a managed care/health plan institution or have managed care as a specialty practice area; 20% had previous coursework or continuing education in pharmacogenomics; and 39% were aware of existing policies on pharmacogenomic tests at their institutions. The average score on the knowledge test was 2.7 (maximum score of 12). Pharmacists who have engaged in prior pharmacogenomic continuing education or coursework scored higher than those without prior education in this area (P<0.0001). Also, pharmacists who have knowledge of existing institutional policies surrounding pharmacogenomics scored higher than those who did not know of or have institutional policies (P<0.0008). Additionally, 46% of the respondents indicated that pharmacists are the best equipped health care provider to receive and interpret pharmacogenomic test results that relate to a patient’s drug therapy management.

| Table: Natalizumab New Users: Pharmacy or Medical Claims for Alternative Multiple Sclerosis (MS) Drugs Found 5 Years Prior to Their Index Natalizumab Claim |
|----------------------------------|------------------|------------------|------------------|
|                                   | 6-Month Continuous Enrollment (n = 209) | 24-Month Continuous Enrollment (n = 141) | 60-Month Continuous Enrollment (n = 38) |
| Glatiramer (Copaxone)             | 41 (19.6%)       | 39 (27.7%)       | 13 (34.2%)       |
| Interferon beta-1a (Rebif)       | 24 (11.5%)       | 33 (23.4%)       | 12 (31.6%)       |
| Interferon beta-1a (Avonex)      | 19 (9.1%)        | 25 (17.7%)       | 12 (31.6%)       |
| Interferon beta-1b (Betaseron)   | 23 (11.0%)       | 20 (14.2%)       | 5 (13.2%)        |
| Any of the above                  | 103 (49.3%)      | 86 (61.0%)       | 28 (73.7%)       |
| No alternative MS agent           | 106 (50.7%)      | 55 (39.0%)       | 10 (26.3%)       |

*aNew start to natalizumab was defined as no natalizumab claim in the 6 months prior to the index claim. No member had a claim for fingolimod or mitoxantrone in the follow-up periods.
CONCLUSIONS: The findings in this study indicate that pharmacists are more likely to answer correctly about approved oncology-related pharmacogenomic tests if they have previous education and are exposed to policies dealing with pharmacogenomics at their workplace. However, for the overall target population, there is still a great need for pharmacy continuing education and training programs in this area.

SPONSORSHIP: This research was conducted by OptumInsight, Minneapolis, MN, without external funding.

Existence and Impact of Geographic Access-Spillover on Drug Sales

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BACKGROUND: We have conducted this study to provide a resource for interested parties, since managed care organizations (MCOs) and pharmaceutical manufacturers increasingly request research surrounding the impact of managed care formulary coverage on access-spillover. Spillover is the enhancement in product sales expected to be observed in a particular geography that occurs when prescribers in that geography choose to prescribe a specific product over competing products because prescribers perceive that their patients are likely to enjoy preferred formulary coverage and thus reduced patient cost burden for that product. Interest in this phenomenon is particularly pronounced given its implications for increased magnitude of manufacturer pricing rebates that may be offered to MCOs in return for a product’s preferred formulary access.

OBJECTIVE: To confirm the existence of the geographic access-spillover effect and evaluate its magnitude in a specific situation.

METHODS: By examining prescription data from a prominent national MCO, which allows preferred formulary access for a metabolic product, we calculated MCO-specific product market share against product competitors across multiple geographies, each of which had different percentage levels of overall preferred access in each specific geography. We repeated this analysis using prescription data from a second national MCO that allows nonpreferred formulary access to the same product. For each of these two datasets, market share of the metabolic product was plotted against the percentage of overall preferred access in each geography, and regressions were created to calculate the incremental impact of the product’s geographical preferred access levels on the product’s MCO-specific market share.

RESULTS: The slopes of MCO-specific product market share versus geographical preferred access were 0.34% and 0.54% market share per percentage levels of overall preferred access in each specific geography. The slopes of MCO-specific product market share versus nonpreferred access, respectively (P=0.009, P=0.008).

CONCLUSIONS: The positive relationship between the product’s preferred geographical formulary access and increased MCO-specific market share at both the MCO preferring the product and MCO not preferring the product provides evidence in support of the existence of an access-spillover effect. Additionally, the slopes of the market share regressions provide some indication of the magnitude of this effect’s impact when applied to the MCO-specific market share of a product in both a preferred and nonpreferred formulary position.

SPONSORSHIP: This research was conducted by SkyLaunch Advisors, New York, NY, without external funding.

Final Results from the Multicenter COMPACT Study of Complications in Patients with Sickle Cell Disease and Utilization of Iron Chelation Therapy: A Retrospective Medical Records Review

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BACKGROUND: Despite declining mortality, complication rates remain high among adult sickle cell disease (SCD) patients. Previous studies suggest that caring for adults with SCD is a major challenge in the United State, since patients often become disconnected from the health care establishment when transitioning from pediatric care due to the paucity of adult providers knowledgeable in SCD and fragmentation in coordinated care. Consequently, inpatient hospitalizations (IP) and emergency room (ER) visits among adult SCD patients may be higher than expected. Resource use data among adult SCD patients is scant.

OBJECTIVE: To evaluate transfusion burden, complication rates, chelation (ICT) patterns, and associated resource utilization in SCD patients ≥16 years with a focus on young adults (16-30) in order to understand the impact on health outcomes during the transition from pediatric to adult care.

METHODS: Medical records of 254 SCD patients ≥16 were retrospectively reviewed between August 2011 and July 2012 at three U.S. tertiary care centers. Patients were classified into cohorts based on cumulative units of blood transfused and history of ICT: <15 units and no ICT (Cohort 1 [C1]), ≥15 units and no ICT (Cohort 2 [C2]), and ≥15 units and receiving ICT (Cohort 3 [C3]). SCD complication rates were expressed as the number of SCD complications per patient per year (PPPY); rate ratios (RRs) were used for cohort comparisons. For the young adult subset, only complications and resource utilization observed between ages 16 and 30 were analyzed.

RESULTS: The transfusion rate decreased from 10.9 units PPPY at age 16 to 1.0 unit PPPY at age 45. The rate (95% CI) of any SCD complications PPPY was highest in C2. 3.02 (2.89-3.14), followed by C3. 2.26 (2.16-2.37), then C1. 1.66 (1.54-1.77). In patients ≥16, pain was the most frequent complication and the most common reason for IP (76%) and ER (82%) visits, followed by infections IP (6.3%) and ER (6.5%). Infections were more prevalent in young adults (ER [8%], IP [7%]); priapism was more common in patients ≥30 for ER visits (3.4%). Among transfused patients (C2+C3), those receiving ICT were less likely to experience SCD complications than those who did not (rate ratio [RR] [95% CI], C2 vs. C3, OP: 1.39 [1.15-1.68]; IP: 0.94 [0.78-1.14]; ER: 1.50 [1.23-1.83], C2 vs. C3, OP: 0.85 [0.70-1.02]; IP: 1.93 [1.69-2.21]; ER: 2.45 [2.10-2.87]).

CONCLUSIONS: Complication rates and associated IP and ER visits were higher among transfused (C2+C3) SCD patients ≥16 years. Among transfused patients, those receiving ICT were less likely to experience complications than those without ICT. This trend was more pronounced in young adults, suggesting greater vulnerability of this population, potentially due to discrepancy in care as patients transition from pediatric to adult care. These results highlight the need for increased patient and provider education and support through transition and adulthood to reduce the complication burden that may be related to poorly or untreated iron overload in transfused individuals with SCD.
METHODS: To describe formulary decision makers’ perceptions of adherence outcomes studies of such programs were either positive or neutral by a majority of respondents. In order to consider coverage action of a bundled branded product with an adherence program, or neutral by a majority of respondents. In order to consider cover-

OBJECTIVE: To describe formulary decision makers’ perceptions of adherence outcomes studies, drug manufacturer-sponsored adherence programs, the value of these programs, and the influence of program evaluation studies on formulary decisions.

METHODS: Approximately 500 payer decision makers were invited to participate in a web-based survey. To be included in the study, respondents had to (a) be a clinician, (b) work for a health plan, and (c) be directly involved in formulary decision making. The survey consisted of 29 multiple choice or open-ended questions. A case study of the HereToHelp program, a support program for patients taking buprenorphine for opioid dependence, was included as an example of a drug manufacturer-sponsored adherence program. Descriptive statistics were used for data analysis, with results presented as counts and percentages.

RESULTS: A total of 24 respondents met the inclusion criteria and participated in the study (response rate: 4.8%). Respondents were primarily pharmacy directors (87.5%) with an average of 8.2 years in their current positions. Seven respondents (29.2%) indicated they had been presented with outcomes data for programs similar to that in the case study example, with 6 indicating they had utilized those data to make formulary decisions. Over 54% answered they had been directly involved with the analysis of an adherence outcomes study. Two respondents indicated their organizations currently contracted with a drug manufacturer on an outcomes-based contract, and over 70% stated their organizations provided adherence program enrollment to their members. Respondents’ beliefs regarding the impact of drug manufacturer-sponsored adherence programs in reducing overall health plan spending and the credibility of adherence outcomes studies of such programs were either positive or neutral by a majority of respondents. In order to consider coverage action of a bundled branded product with an adherence program, 52.2% stated a >15% improvement in adherence with the program over standard of care would need to be realized. In the event a medication

SPONSORSHIP: This study was funded by Novartis Pharmaceuticals Corporation, East Hanover, N.J.

Abstracts from Professional Poster Presentations at AMCP’s 25th Annual Meeting & Expo

### TABLE Rate and Rate Ratios of SCD Complications by Setting

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<tr>
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<th>All Patients</th>
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<tr>
<td></td>
<td>C1 n = 69</td>
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<td>Rate PPPY [95% CI]</td>
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<td>Rate PPPY [95% CI]</td>
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Patients 16-30

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Outpatient

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<td>Rate PPPY [95% CI]</td>
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Inpatient

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<td>Rate PPPY [95% CI]</td>
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Emergency room

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<td>Rate PPPY [95% CI]</td>
<td>0.77 [0.66 - 0.89]</td>
<td>1.27 [1.16 - 1.38]</td>
<td>0.52 [0.45 - 0.58]</td>
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C = cohort; CI = confidence interval; PPPY = per patient per year; RR = rate ratios; SCD = sickle cell disease; SD = standard deviation.

**SPONSORSHIP:** This study was funded by Novartis Pharmaceuticals Corporation, East Hanover, N.J.

**Formulary Decision Makers’ Perceptions Regarding Value of Adherence Programs and Associated Outcomes Studies**

White NP, Olvey E,* Rice GK. NucleusX Market Access, 2 Ravinia Dr., Ste. 605, Atlanta, GA 30346; eleanor.olvey@nucleux.com, 404.443.1611

**BACKGROUND:** Three-quarters of Americans who take prescription medications have been reported to be nonadherent to their regimens in 1 or more ways. The clinical and economic impact of nonadherence continues to be significant, with an estimated cost of over $100 billion annually to the health care system. Programs designed to improve adherence are at the forefront of efforts to improve outcomes; however, the perceived value formulary decision makers place on these programs and the studies conducted to evaluate the effectiveness of these interventions remains unclear.

**OBJECTIVE:** To describe formulary decision makers’ perceptions of adherence outcomes studies, drug manufacturer-sponsored adherence programs, the value of these programs, and the influence of program evaluation studies on formulary decisions.

**METHODS:** Approximately 500 payer decision makers were invited to participate in a web-based survey. To be included in the study, respondents had to (a) be a clinician, (b) work for a health plan, and (c) be

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became generically available, 47.8% stated they would consider continued coverage of the bundled branded product plus adherence program if presented with a robust outcomes study demonstrating superior impact on adherence. A concern most frequently highlighted as possible bias to study results was manufacturer involvement and influence.

CONCLUSIONS: Most payer decision makers were positive or neutral about the impact drug manufacturer-sponsored adherence programs may have in reduction in spending and the credibility or believability of the associated outcomes studies. However, if presented with robust data, most were willing to take some coverage action.

SPONSORSHIP: This research was conducted by NucleusX Market Access, Atlanta, GA, without external funding.

■ Gender Differences in Health-Related Quality-of-Life and Kessler 6 Index for Patients with Alzheimer’s Disease in the United States

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BACKGROUND: Alzheimer’s disease (AD) is the sixth leading cause of death in the United States, affecting more than 5 million of the American geriatric population. Gender tends to play an important role in AD for many factors including disease progression, psychological well-being, and health-related quality of life (HRQOL).

OBJECTIVE: To examine gender differences in HRQOL using the Short-Form 12 (SF-12) and the Kessler index (K6) for Medicare beneficiaries with AD in the U.S. civilian noninstitutionalized population.

METHODS: A cross-sectional analysis was conducted using the national Medical Expenditures Panel Survey data (MEPS). Study subjects included patients who reported having Medicare as well as receiving at least 1 FDA-approved AD prescription drug in U.S. outpatient settings during 2009. The dependent variables for the analyses were 18 variables describing HRQOL outcomes from SF-12 and K6 questionnaires. A series of weighted Wald chi-square statistics were used to test the effect of gender on each variable. Weighted univariate statistics also were applied to examine gender differences in overall mental (MCS) and physical components (PCS) scores. All analyses were accomplished by taking into consideration the MEPS sample weight, stratification, and clustering variables by SAS 9.22 analytical software.

RESULTS: There were an estimated 42.49 million Medicare recipients from 2009 MEPS, of which 1.4 million (3.33%) patients received at least one AD prescription during an outpatient visit. The majority of the AD patients were female (64.03%) with an average age of 78.8. Comparison of MCS for male (M = 44.5, SE = 1.93) and female (M = 44.9, SE = 1.32) revealed no significant differences between the groups (P = 0.85). In comparison with PCS, males illustrated higher physical scores (M = 36.6, SE = 1.97) than females (M = 32.4, SE = 1.28). However, there is no significant difference between the groups (P = 0.06). The results from the (K6) also showed no significant difference in psychological distress measures between male and female AD patients. All mean HRQOL scores (PCS, MCS, K6) in both male and female AD groups were lower than the national norm of 50.

CONCLUSIONS: The study findings indicated that HRQOL in AD is impaired, but with no significant differences between male and female in both the SF-12 and K6 among Medicare AD patients. Two factors may explain the findings: (a) Given AD has been undersampled in the MEPS database, a significant difference may not be established, and (b) limitations of using the SF-12 questionnaire in mental health. However, our study makes a significant contribution in providing a broader picture of HRQOL and psychological distress of AD from national representative data.

SPONSORSHIP: This research was conducted by Nova Southeastern University, Fort Lauderdale, FL, without external funding.

■ Health Care Costs Among Asthma Patients on Budesonide/Formoterol Combination and Fluticasone/Salmeterol Combination

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BACKGROUND: The impact of different inhaled corticosteroid and long-acting beta agonist (ICS/LABA) combination treatments on health care costs among asthma patients remains uncertain.

OBJECTIVE: To evaluate the impact of different ICS/LABA combination therapies on asthma-related and all-cause costs among asthma patients in a U.S. managed care population.

METHODS: From HealthCore Integrated Research Database, asthma patients aged 12-64 years, who initiated budesonide/formoterol combination (BFC) or fluticasone/salmeterol combination (FSC) between June 1, 2007, and September 30, 2010, were identified and matched using propensity score methods. Patients who previously used ICS/LABA combination therapy were excluded. Asthma-related and all-cause resource utilization and costs were estimated during the 12-month pre/post ICS/LABA treatment initiation. Gamma regression was used for cost assessment.

RESULTS: Of the 3,122 BFC and 8,177 FSC patients identified, 3,043 BFC and FSC patients were matched. Cohorts were well balanced on all baseline characteristics and pre-index asthma medication use; however, there was a difference in pre-index average total cost ($7,416 for BFC vs. $8,031 for FSC [95% unadjusted CI, −$970, −$244]) and in asthma-related cost ($1,818 for BFC vs. $1,964 [95% unadjusted CI, −$238, −$48]) and in asthma-related inpatient costs ($341 for BFC vs. $434 [95% unadjusted CI, −$137, −$44]). During the 12 months after initiation, asthma-related emergency department costs were higher within BFC patients (mean difference, $14 [95% CI, $2, $29]), while asthma-related inpatient hospitalization costs were higher within FSC patients (mean difference $37, −$44, −$29). Among patients with ≥1 hospitalization, average inpatient costs were found to be significantly higher in the FSC cohort (mean difference, $6,254 [95% unadjusted CI, −$3,419]). The all-cause health care cost was lower for BFC patients (mean difference, $945 [95% CI, −$1,321, −$553]).

CONCLUSIONS: This is the first U.S. study to use administrative claims data to compare health care costs for asthma patients receiving BFC or FSC. In this study, average total cost of care was increased after initiation of therapy in both cohorts, with the increase being more pronounced in FSC patients. BFC treatment was associated with comparable asthma-related health care costs with FSC during the 12 months after initiation.

SPONSORSHIP: This research was conducted by AstraZeneca LP, Wilmington, DE, without external funding.

■ Health Care Expenditure Burden Among Elderly Patients with Cancer

Shah D, Khán N,* Tongram V. Oxford Outcomes, an ICON plc company, 161 Madison Ave., Ste. 205, Morristown, NJ 07960; Nasreen.khan@iconplc.com, 505.977.0671
BACKGROUND: It is estimated that about 1.6 million men and women in the United States will be diagnosed with cancer of all sites in 2012. Prevalence of cancer and associated mortality is higher in the elderly population. With the increasing health care costs, payers are interested in understanding the economic burden of cancer and factors associated with the high cost of cancer.

OBJECTIVE: To examine the health care utilization and expenditure burden in elderly patients with cancer.

METHODS: We used Medicare Current Beneficiary Survey (MCBS) Cost and Use file from years 2000 to 2007. The survey, which is also linked to the claims data, provides information on elderly health care use, expenditure, and demographic characteristics. Patients with cancer were identified from self-reports for the diagnosis. The following measures of utilization and expenditure were assessed: all-cause hospitalization, outpatient visits, and total (sum of hospitalization and outpatient) expenditure. Multivariate Poisson regression models (for number of visits) and generalized linear models with log link and gamma family (for expenditure data) were used to assess the effect of patient's characteristics on inpatient, outpatient, and total expenditure.

RESULTS: In the years studied, about 15,725 patients were reported with a cancer diagnosis. Of these, 50.0% were female; 95.4% were white; 20.9% had no high school education; 62.6% were married. The average income was about $38,063 (SD $79,857), and mean age was 76 years. Average number of outpatient visits was 4.8 (SD 8.5), and average number of hospitalization was 0.33 (SD 0.81) per year. In multivariate regression (Poisson) models, number of outpatient visits were higher for females ($P < 0.001$), those in poor health ($P < 0.001$), and among elderly with college education ($P < 0.001$), whereas inpatient visits were lower among females ($P = 0.015$), college education had no effect ($P = 0.689$); and those in poor health had higher expenditure ($P < 0.001$). Mean total expenditure in this population was about $7,888 (SD $14,004) per year. In multivariate regression models, females had lower expenditure compared with males ($P = 0.020$), and higher education had no statistically significant effects, where those in poor health reported statistically significant higher expenditure ($P < 0.001$).

CONCLUSIONS: Studies have indicated that Medicare beneficiaries with cancer have higher expenditure compared with similar noncancer patients. From this study, we found that gender, health status, and education level were important predictors of health care utilization among elderly cancer patients. Not surprisingly, those in poor health had higher health care expenditures. We also found that outpatient and hospitalization are not always complementary, and higher outpatient visits may actually act as a substitute for more costly hospitalization.

SPONSORSHIP: This research was conducted by Oxford Outcomes, an ICON plc company, Morristown, NJ, without external funding.

Health Care Resource Utilization Following Initiation of a Triptan

Messali A,* Owens G, Bloudek L, Kori S, Cole A, Chia J. Allergan, Inc., 2525 Dupont Dr., Irvine, CA 92612; Messali@usc.edu, 858.335.9681

BACKGROUND: Triptans are often the first prescription treatment chosen for patients suffering from migraines. The efficacy of triptans has been established in clinical trials, but real-world evidence has shown that adherence and persistence rates are generally poor. Measuring the impact of initiating a triptan on health care resource utilization (HRU) is a potential way of measuring the value of these medications outside of the clinical trial setting.

OBJECTIVE: To measure changes in the utilization of medical services and prescription medications following initiation of a triptan.

METHODS: A large, nationally representative database of medical and pharmacy claims was used to identify patients with a diagnosis of migraine who had recently begun triptan therapy. As a secondary analysis, results were stratified by the number of triptans used and option for the elderly and the renally impaired patient, an assessment of the resource use and costs among these subgroups will be of value to health care decision makers treating these special populations of patients with unmet medical needs.

OBJECTIVE: To compare health care resource use and cost outcomes among T2DM patients who initiate therapy with saxagliptin or an sulfonylurea (SU) during the 6-month period following treatment initiation and to assess outcomes among subsets of (a) patients with renal impairment, (b) those aged 65 and older, and (c) aged 75 and older.

METHODS: This retrospective analysis of adults with T2DM who initiated saxagliptin or an SU during Q1 2009-Q2 2011 utilized the MarketScan U.S. health care claims database. Patients who had no prescriptions for saxagliptin or an SU during the 6 months prior to index were followed for 6 months after initiating the study drug to assess health care resource use and cost outcomes. All-cause and diabetes-related health care resource use, health care costs, and patient characteristics were compared. Subgroups of interest included T2DM patients who were >65 years, >75 years, and renally impaired. Multivariate logistic regression models were utilized to evaluate the impact of key characteristics on outcomes.

RESULTS: There were 168,498 T2DM patients included in the study, of which 13,929 were initiators of saxagliptin, and 117,756 were initiators of an SU. Saxagliptin patients were significantly less likely than SU patients to have inpatient hospitalizations or emergency room visits during the study period ($P < 0.001$). Saxagliptin patients were more likely to have outpatient and other medical visits and had more use of antidiabetic medication in the study period ($P < 0.001$). Total health care costs during the study period were $554 lower for saxagliptin than SU patients ($7,346 vs. $7,900; $P < 0.001$). Results of the subgroup analyses of patients >65 and patients >75 revealed statistically similar findings to the overall analysis. Results of patients with renal impairment were also similar, but cost levels were greater than costs for the overall sample ($10,638 vs. $15,371; $P < 0.001$).

CONCLUSIONS: In a database reflective of clinical practice in the United States, saxagliptin patients were significantly less likely than SU patients to have inpatient hospitalizations or emergency room visits. While saxagliptin patients had more outpatient visits and antidiabetic medication use, total medical costs were less for saxagliptin patients than for SU patients.

SPONSORSHIP: This research was funded by Bristol-Myers Squibb, Plainsboro, NJ.
by concomitant opioid use. The first diagnosis of a migraine occurred must have occurred at least 12 months before initiation of the triptan. The post-triptan time period was then made equal to each patient’s time between first diagnosis and first triptan fill. Observed health care resources included physician office visits, emergency room (ER) visits, hospitalizations, diagnostic imaging, and select prescription drugs (opioids, acetylsalicylic acid/NSAIDs, medications used as migraine prophylaxis).

RESULTS: The sample consisted of 9,521 patients, 18.9% of whom tried more than one triptan during follow-up. Triptan initiation was not associated with a significant reduction in HRU. Among patients who used 2 unique triptans, the rates of ER visits and hospitalizations were significantly higher during the post-triptan period (P = 0.01 and P = 0.02, respectively). Among all patients, triptan initiation was followed by significant increases in the average number of fills for opioids (P < 0.01), acetylsalicylic acid/NSAIDs (P < 0.01), and migraine prophylaxis medications (P < 0.01). Patients who used concomitant opioids were more likely to use the ER (P < 0.01) or be hospitalized (P < 0.01). Concomitant opioid users also filled more acetylsalicylic acid/NSAIDs (P < 0.01) and migraine prophylaxis medications (P < 0.01), compared with nonopioid triptan users.

CONCLUSIONS: Our results show that the use of triptans does not reduce HRU. Particularly among patients who switched triptans and patients who used opioids concomitantly with their triptan, significant increases in pharmacy and medical utilization were seen. Further research is needed to better understand persistence and satisfaction with triptans, both of which may be drivers of HRU.

SPONSORSHIP: This research was conducted by Allergan, Inc, Irvine, CA, without external funding.

Hepatitis C Specialty Drug Utilizers Cost of Care Trends 2008 to 2011: An Integrated Medical and Pharmacy Claims Analysis

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BACKGROUND: The 2011 FDA approval of protease inhibitors (boceprevir and telaprevir) to treat hepatitis C (Hep C) resulted in the Hep C treatment recommendation becoming triple therapy with a protease inhibitor, alpha interferon, and ribavirin. Health plans need an understanding of Hep C total cost of care and specialty drug cost trends in order to prioritize clinical and utilization management program development.

OBJECTIVE: To describe the cost of care trends among commercially insured individuals utilizing a Hep C specialty drug stratified by specialty and nonspecialty costs within the medical and pharmacy (Rx) benefits.

METHODS: Integrated Rx and medical claims data from 1.2 million commercially insured members were queried. Members were required to be age 0 to 64 and continuously enrolled for a full year during 2008, 2009, 2010, or 2011. Presence of a Hep C diagnosis was defined as the following: (a) 2 or more medical claims with a Hep C ICD-9-CM diagnosis code; (b) 1 medical claim with Hep C and one Hep C drug claim; or (c) 2 or more Hep C drug claims. Only those drugs approved by the FDA for Hep C were used in the diagnosis criteria and included the following: boceprevir, peginterferon alfa-2a, peginterferon alfa-2b, ribavirin, and telaprevir. Each year the prevalence of members with a Hep C diagnosis and the subset with a Hep C specialty drug claim were identified. Among members using Hep C specialty drugs, the average per patient per year total cost of care was calculated. Total cost of care was separated into 4 categories: medical Hep C specialty drug, medical all other, pharmacy Hep C specialty drug, and pharmacy all other.
**BACKGROUND:** The immunosuppressant calcineurin inhibitors cyclosporine (Neoral, Sandimmune, Gengraf) and tacrolimus (Prograf, Hecoria) are frequently used to reduce the risk of rejection after organ transplant. Calcineurin inhibitors represented approximately 50% of the $0.48 per member per month immunosuppressant spend in 2011 among Prime Therapeutics’ 9 million commercially insured lives. Medication waste, as a result of a drug switch, is a concern for prescriptions, especially with supplies beyond the traditional 30 days. Immunosuppressant pharmacotherapy frequently requires a combination of drugs; however, only 1 calcineurin should be used at a time. Switching between calcineurins could result in medication waste.

**OBJECTIVE:** To examine and quantify the presence of calcineurin inhibitor waste associated with these channels: retail 30 days supply (DS), retail 90 DS, and mail order 90 DS.

**METHODS:** Among 9 million commercially insured members, first calcineurin claims were identified during January 1, 2011, to June 30, 2011, and defined as index drugs and dates. Members with an index calcineurin claim were then followed until their disenrollment date or the end of 365 days follow-up, whichever occurred earlier. All calcineurin claims were queried during the follow-up period and categorized as retail 30, retail 90, or mail 90. An end date for each claim was defined as fill date plus days supply. During the post-index claim analysis period, the presence of an overlapping days supply with the alternative calcineurin agent was defined as waste. Days of overlap waste was quantified, and average days waste per claim within a channel was calculated. The prevalence of waste by channel was statistically compared using the chi-square Fischer's Exact test. Members' medical claims ICD-9-CM codes were queried during the follow-up for presence of linezolid and any other antibiotics. The following occurred were assessed during the 30-day follow-up: linezolid claim, other antibiotic claim, hospitalizations, ER visits, all outpatient pharmacy and medical. For both groups, all pharmacy and medical claims with waste were queried in the previous 6 months and 30-day follow-up for presence of linezolid and any other antibiotics. The following outcomes were assessed during the 30-day follow-up: linezolid claim, other antibiotic claim, hospitalizations, ER visits, all outpatient visits, total medical and pharmacy costs, and linezolid costs. Infectious disease diagnoses from medical claim ICD-9-CM codes in the 6 months prior to the index date were hierarchically ranked. Comparisons were performed with the ANOVA test for normally distributed continuous variables, the chi-square test for categorical variables, the Wilcoxon rank sum test for counts, and the Likelihood ratio test on expenditures comparisons.

**RESULTS:** In the intervention group, 217 (2 per 10,000) members had a rejected linezolid claim during June 1, 2011, to June 30, 2011, and 185 (85.3%) met continuous enrollment criteria. The comparison group had

<table>
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<th>Clinical and Economic Outcomes During 30-Day Follow-Up</th>
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<tbody>
<tr>
<td></td>
<td>Intervention (n = 185)</td>
</tr>
<tr>
<td>Age, mean (SD)</td>
<td>46 (17)</td>
</tr>
<tr>
<td>Male</td>
<td>94 (50.8%)</td>
</tr>
<tr>
<td>Linezolid claim</td>
<td>99 (53.5%)</td>
</tr>
<tr>
<td>Other antibiotic claim</td>
<td>58 (31.4%)</td>
</tr>
<tr>
<td>No antibiotic claim</td>
<td>28 (15.1%)</td>
</tr>
<tr>
<td>Average linezolid cost per member, $ (SD)</td>
<td>1,192 (1,478)</td>
</tr>
<tr>
<td>Average number of outpatient visits (SD)</td>
<td>3 (2.1)</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>27 (14.6%)</td>
</tr>
<tr>
<td>Emergency room visit</td>
<td>34 (18.4%)</td>
</tr>
<tr>
<td>Pharmacy and medical total costs, $ (SD)</td>
<td>7,943 (18,429)</td>
</tr>
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</table>

SD = standard deviation.
RESULTS: A total of 393,640 members were evaluated by the edit in the 6-month post-period, with an 84% POS approval rate (328,946 members with approvals). Of the 64,694 members with claims denied at POS, 13% (8,478) were approved at the call center. The number of SA narcotic combination prescriptions exceeding the set quantity limits decreased by 97%; however, the number of targeted claims lacking an appropriate diagnosis rose 3%. Members using more than 2 pharmacies for SA narcotic combination prescriptions decreased by 5%, and those using three or more prescribers for these prescriptions decreased by 8%. Overall, the total number of targeted prescriptions decreased by 3% with an average cost savings per prescription of $0.46. Emergency room utilization decreased 8%, resulting in a savings of $0.93 per member per month.

CONCLUSIONS: Implementation of an automated prior authorization edit for SA narcotic combination agents resulted in more clinically appropriate use of these agents, lowered the risk of doctor and pharmacy shopping habits, and decreased emergency room utilization.

SPONSORSHIP: This research was conducted by Xerox State Healthcare, LLC, Richmond, VA, without external funding.

Impact of Copayment Escalations on Simvastatin Users: Multi-Year Longitudinal Assessment in the MarketScan Commercial Database

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BACKGROUND: Copays for prescription medications are rising as health plans attempt to rein in mounting costs and to shunt drug utilization towards preferred agents. However, patients may respond to the increased price by reducing use of necessary medications.

OBJECTIVE: To estimate the reduction in adherence and medication supplied for patients that experience increases in average monthly copay over time for the chronic lipid management drug simvastatin. Outcome measures were the medication possession ratio (MPR) and days supplied per year.

METHODS: Age-, gender-, health plan type-, plan category-, geographic location-, comorbidity-, and year-adjusted regression analyses were obtained from the nationally representative MarketScan Commercial Claims Database for the years 2007 to 2010 using Generalized Estimating Equations (GEE) for correlated data. This database captures nearly 40 million covered lives in all geographic regions of the United States with claims from self-insured employers and health plans. Included subjects were U.S. residents ages 18 to 64 with continuous enrollment in a health plan for at least 2 years. Users of simvastatin with a minimum of 30 days supplied and at least 2 medication fills annually for a minimum of 2 consecutive years were included. Correlation structure for GEE models was evaluated using the Quasi-Likelihood

In this study, we examined the impact of copayment increases on simvastatin use among patients in a national health plan. We found that increases in copayments led to a reduction in simvastatin adherence and supply. These results highlight the need for further research to understand the clinical impact of copayment increases and to develop strategies to mitigate their effects on patient outcomes.
Information Criterion. Comorbidity was assessed via the Quan revision of the Charlson Comorbidity Index for ICD-9-CM codes (Quan Score). All analyses were performed using SAS 9.3. Statistical significance was set at P < 0.05

RESULTS: A total of 735,590 patients were included in the analysis in the 4 years examined. The mean age in years ± standard deviation (SD) was 53.0 ± 7.3. The mean copayment per month ± SD for simvastatin was $5.92 ± 4.92. The mean MPR ± SD for simvastatin was 0.90 ± 0.17. The mean Quan score ± SD was 0.18 ± 0.47. Increase in $5 or more for average monthly copay was associated with a statistically significant change in MPR of -0.024 (95% CI, -0.026, -0.022). Assuming 365 days of use, this represents a reduction of 8.8 medication days supplied per year. Increase in $10 or more resulted in a change in MPR of -0.034 (95% CI, -0.038, -0.030) representing a reduction of 12.4 medication days supplied per year.

CONCLUSIONS: Copay increases were associated with significant reductions in adherence of the chronic lipid management medication simvastatin. Benefit managers should factor in the possible reduction in necessary consumption when proposing increases in copay structures.

SPONSORSHIP: This research was conducted by Western University of Health Sciences College of Pharmacy, Pomona, CA, without external funding.

Impact of Medical Policy Implementation for Branded Oral Acne Antibiotics on Prescription Utilization and Expenditures

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BACKGROUND: Oral doxycycline and minocycline are standard of care for moderate to severe forms of acne vulgaris and acne rosacea. There are no studies comparing efficacy and safety of branded orally administered minocycline and doxycycline to generic alternatives. A medical policy was implemented to encourage cost-effective therapy through generic utilization and reduction in associated expenditures.

OBJECTIVE: To evaluate the impact of a medical policy program for branded oral acne antibiotics on generic utilization rate (GUR), use of alternative therapy, and total cost of care.

METHODS: This is a retrospective analysis of pharmacy and medical claims data for privately insured members in a midwestern state. Members were required to have a pharmacy claim for an oral antibiotic claim in 2010, a medical claim with an ICD-9-CM code for acne vulgaris or rosacea, and continuous enrollment during the calendar years of 2010 (baseline) and 2011 (follow-up). Pharmacy claims for oral antibiotics that were less than a 28-day supply were excluded from the analysis. To assess the impact of the policy, data for 1 year post-implementation was compared with data 1 year prior. Measures evaluated were amount allowed per member per month (PMPM), amount allowed per claim, and GUR. The primary outcome was to assess differences in these measures with the utilization of oral tetracycline medications after the policy became effective. Secondary outcomes were associated differences in use of topical agents and oral retinoids. T-test was used to measure amount allowed PMPM and amount allowed per claim, and chi-square analyses were used to measure GUR.

RESULTS: There were significant decreases in amount allowed PMPM ($57.78 to $13.73; P < 0.001), amount allowed per claim ($202.50 to $46.30; P < 0.001), and a significant increase in GUR (69.3% to 96.8%; P < 0.001) for the oral antibiotic tetracyclines. For the total cost of care, there was a significant reduction in amount allowed PMPM ($53.22 to $31.95; P < 0.001) and amount allowed per claim ($164.00 to $96.90; P < 0.001). Overall, GUR increased from 59.5% to 73.6% (P < 0.001).

CONCLUSIONS: Since the implementation of the medical policy on the use of branded oral antibiotics in 2011, there was a significant increase in GUR and cost savings associated with less branded antibiotic use.

SPONSORSHIP: This research was conducted by BlueCross and BlueShield of Nebraska, Omaha, NE, without external funding.

Impact of Offering Voluntary and Mandatory Mail Pricing Options at a Retail Pharmacy Network for Employer Groups

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BACKGROUND: Utilization of mail service pharmacies continues to be an effective means to lower prescription costs for employers as well as improve adherence rates. In a 2011 survey, 60% of employers also utilized a plan design that offered 90-day supplies of maintenance medications at retail pharmacies in addition to mail service. For labor unions in particular, managing costs for prescription medications while also providing plan participants with increased choice and convenience is effective. By offering a coalition of union clients a continuum of retail pharmacy 90-day plan design options from voluntary to mandatory ultimately translates into reduced drug spend and flexibility for plan participants.

OBJECTIVE: To evaluate the impact on prescription costs and adherence rates by implementing voluntary or mandatory benefit designs where plan participants can receive 90-day prescriptions for maintenance medications.

METHODS: An observational pre- and post-implementation study using pharmacy claims data over 24 months from an integrated database. For the study, cost and adherence metrics were evaluated for a subset of a 300,000 life nationwide coalition trade union. Channel shifts and any associated financial savings were assessed among the groups that implemented either mandatory or voluntary 90-day plan designs at a retail pharmacy.
RESULTS: Results indicated gross savings of approximately 1% to 3% with 20%-25% of maintenance 30-day prescriptions moving to 90-day for those clients with a mandatory 90-day plan design with a retail component. Savings of less than 1% were expected with 10%-15% of maintenance 30-day prescriptions moving to 90-day for those clients with a voluntary 90-day plan design with a retail component. Medication possession ratio (MPR) improved comparing pre- and post-periods, which supports prior literature that 90-day prescriptions and interactions with retail pharmacists improve overall adherence rates.

CONCLUSIONS: Managing prescription drug costs as well as improving medication adherence continues to be very important for employers, particularly union groups that are sensitive to high costs and significant member disruption. By offering employers options in implementing a less restrictive voluntary 90-day plan design that allows for member outreach to a more restrictive mandatory 90-day plan design, this results in prescription cost savings, improved adherence rates, and flexibility for clients sensitive to member disruption.

SPONSORSHIP: This research was conducted by CVS Caremark, Northbrook, IL, without external funding.

Impact of Polypharmacy on Health Care Utilization Among the Elderly Population: Evidence from National Data from 2005-2008

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BACKGROUND: The elderly population is increasing with higher prevalence of multiple diseases that must be managed concurrently. Polypharmacy is also prevalent in the elderly population, as health providers seek to manage these diseases with multiple medications. It is also recognized that polypharmacy increases risk of adverse effects, drug/drug interactions, and drug/disease interactions and could have huge economic implication in the form of hospital visits and health care expenditures.

OBJECTIVE: To evaluate the impact of polypharmacy on national health care utilization in patients aged ≥65.

METHODS: This study used the Medical Expenditure Panel Survey (MEPS), a nationally representative panel survey, which provided data from 2005-2008. Polypharmacy was defined as 5 or more medications. Health care utilization variables (physician office visits, emergency room (ER) visits, and expenditures) were analyzed separately in evaluating their relationship to polypharmacy. Visits were modeled using a weighted negative binomial regression, while expenditures were modeled using a generalized regression model. All models were adjusted for patient demographic and socioeconomic factors. National estimates for patients were estimated using weights provided by MEPS. The weighted multivariate logistic model was used to determine factors affecting multiple medication use.

RESULTS: A sample of 4,629 records represented a total of 99,126,153 weighted individuals (mean age, 74.7; SE=0.138). The southern region represented 37.3%, women 58.1%, Caucasians 87.3%, and 56.8% were married. Approximately 69.4% of patients were on 5 or more medications with the most prevalent disease being hypertension (62.7%). Polypharmacy patients had a significantly greater number of mean differences in physician office visits 3.69 (SE=0.09), ER visits 0.103 (SE=0.0001), office-based total expenditures $725 (SD=1.29), and total prescription expenditures $500 (SD=3.23) annually compared with patients on <5 medications. A logistic model reported females were 1.25 (OR=1.25), 1.04 (1.49) times more likely to be affected by polypharmacy, and patients with hypertension are 3.3 (OR=3.30; CI: 2.78-3.92) times more likely to experience polypharmacy.

CONCLUSIONS: This study identifies that polypharmacy affects health care utilization among elderly patients. Polypharmacy patients incur increased physician and ER visits and spend more on medications. Medication management with a focus on reducing polypharmacy for elderly patients could simplify drug regimens and potentially reduce harm.

SPONSORSHIP: This research was conducted by University of Missouri-Kansas City School of Pharmacy, Kansas City, MO, and University of Texas School of Medicine, San Antonio, TX, without external funding.

Impact of Refill and Save Program on Adherence to Desvenlafaxine and Health Care Costs

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BACKGROUND: Major depressive disorder (MDD) is characterized by consistent depressed mood, fatigue, lack of interest in activities, insomnina or hypersomnia, and other symptoms that negatively affect quality of life and productivity. The annual and lifetime prevalence rates of MDD in the United States are 7% and 17%, respectively. Desvenlafaxine (DSV), a serotonin-norepinephrine reuptake inhibitor, is 1 of multiple antidepressants indicated for MDD. Good adherence to antidepressants has been shown to be associated with better outcomes; yet, adherence to antidepressants in general is poor. A large U.S. health plan began a “Refill and Save Program” (RSP) in October 2009 to promote better adherence. The RSP linked a copayment discount directly to adherence by reducing the health plan member copayment (discount = $20 retail, $50 mail order) for DSV prescriptions when refilled within 30 days of the end of a previous antidepressant fill.

OBJECTIVE: To understand the effect of RSP copayment discounts for DSV on medication adherence and health care costs by comparing health plan members with and without RSP benefits.

METHODS: This retrospective claims database analysis examined commercially insured members aged 18 years old or older. The index date, set during the first 6 months of the RSP (October 2009-March 2010), was the first DSV fill with RSP benefit for the RSP cohort, and the first DSV fill for the non-RSP cohort. Members were continuously enrolled for 6 months pre-index (baseline) and 9 months post-index (follow-up). Outcomes measured during follow-up were proportion of days covered (PDC) with DSV and total health care costs (health plan and patient paid costs for all medical services and outpatient prescription medications). The relationship between RSP and PDC was modeled using ordinary least-squares regression; costs were modeled using gamma regression with a log link. Models were adjusted for cohort, pre-index antidepressant use (PDC on antidepressants, naive vs. current DSV users, naive antidepressant use), index month, plan characteristics (high deductible, percentage points higher (95% CI=0.831-0.971; P=0.007) in the RSP (vs. non-RSP) cohort.

RESULTS: A total 11,820 members met the criteria: n=7,463 (63.1%) RSP and n=4,357 (36.9%) non-RSP. The mean (SD) age in each cohort was 45 (12) years (P<0.001); 74.3% and 77.9% of the RSP and non-RSP cohorts, respectively, were female (P<0.001). Unadjusted mean (SD) PDC was 0.67 (0.31) in the RSP cohort and 0.58 (0.33) in the non-RSP cohort (P<0.001). Unadjusted mean (SD) total health care costs were $8,406 ($14,163) and $9,176 ($22,832) in the RSP and non-RSP cohorts, respectively (P=0.044). After adjusting for covariates, PDC was 7.4 percentage points higher (95% CI=5.1-8.6; P<0.001) and total health care costs were 10.2% lower (cost ratio=0.898, 95% CI=0.831-0.971; P=0.007) in the RSP (vs. non-RSP) cohort.
Impact of the Affordable Care Act (Health Care Reform) Provisions for Preventive Care Coverage on Pharmaceutical Costs and Utilization

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BACKGROUND: Preventive health care is intended to keep people healthy, avoid or delay onset of disease, help people lead productive lives, and reduce overall health care costs. According to the Affordable Care Act, nongrandfathered plans must provide certain preventive services without member cost sharing when delivered by an in-network provider. For plan years that begin on or after September 23, 2010, the U.S. Preventive Services Task Force recommendations include the use of aspirin, fluorides, folic acid, iron, and tobacco cessation products for preventive health care. With these mandates, pharmaceutical costs and utilization are expected to increase, while overall health care costs and utilization are expected to decrease in the future. It is too soon to evaluate overall health care costs and utilization, while we are now beginning to see the impact of preventive care coverage on pharmaceutical costs and utilization.

OBJECTIVE: To evaluate the effect of health care reform provisions regarding preventive care coverage on pharmaceutical costs and utilization.

METHODS: A retrospective observational study design using pre- and post-implementation data from an integrated database of administrative pharmacy claims was used to evaluate the impact of health care reform provisions around preventive care on pharmaceutical costs and utilization. The analysis was performed on the membership of nongrandfathered employer plans composed of 1.4 million members. For the clients in this observational study, these health care reform provisions were implemented in 2011. Pharmaceutical costs and utilization were analyzed for aspirin, fluorides, folic acid, iron, and tobacco cessation products (preventive drugs). The metrics used to measure cost and utilization changes included utilization of preventive drugs as a percentage of average member, preventive drug gross cost per member per year (PMPY), preventive drug plan cost PMPY, preventive drug days supply PMPY, and preventive drug plan cost as a percentage of total drug plan cost.

RESULTS: Comparison was done between the pre-implementation period of 2010 versus the post-implementation period of 2011. Of the membership, 1.2% utilized a preventive drug in 2011, an increase of 90.2%. Preventive drug gross cost PMPY increased 43.8% to $1.69. Preventive drug plan cost PMPY increased 120.6% to $1.06, which represented less than 0.2% of total drug plan cost. Preventive drug days supply PMPY increased 146.3% to 1.06.

CONCLUSIONS: The study outcomes provide preliminary insight on the impact of health care reform provisions for preventive care coverage of aspirin, fluorides, folic acid, iron, and tobacco cessation products without member cost share on pharmaceutical costs and utilization.

SPONSORSHIP: This research was conducted by CVS Caremark, Northbrook, IL, without external funding.

SPONSORSHIP: This research was funded by Pfizer Inc., New York, NY.

Improving the Participation Rate for Comprehensive Medication Reviews Through Enhancing Part D Beneficiaries’ Understanding of the Service

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BACKGROUND: The Centers for Medicare and Medicaid Services (CMS) requires Part D sponsors to offer a comprehensive medication review (CMR) annually to eligible Part D beneficiaries through the plans’ Medication Therapy Management Program (MTMP). In 2011, the Pharmacy Quality Alliance endorsed “the completion rate for comprehensive medication review” as a quality measure for MTMPs, and it is expected that CMS will adopt this measure into the plan-rating system in 2014 to promote delivery of the service for patients at risk for medication-related problems.

OBJECTIVE: To demonstrate the effectiveness in increasing CMR participation rate of a standardized script that emphasized benefits and potential barriers of receiving a CMR.

METHODS: A new CMR recruitment script, shaped by the Health Belief Model, was developed based on a previous pilot study. This newly developed script aimed to enhance beneficiaries’ understanding of the CMR service, explain the benefits of the service from the beneficiaries’ perspective, and address potential barriers that beneficiaries might have in accepting the service. The new script was tested in the first quarter of the MTMP enrollment in 2012 using a randomized controlled experiment with the original script as the control. The original script, which was used for CMR recruitment in the previous year, described the service but did not emphasize key benefits or barriers from the beneficiaries’ perspective. The CMR service was offered to the MTMP members using the scripts via phone calls by live call agents. Two call attempts were made to reach the person, and if the person could not be reached after 2 attempts, a computer-generated voicemail message was left, and a letter regarding the MTMP and CMR was subsequently mailed.

RESULTS: There were 105,701 beneficiaries in the first quarter of the MTMP enrollment. Approximately 10% responded to the calls and listened to the scripts. Members who responded to calls were on average 68.9 years old, taking 10 to 11 chronic medications, and with 6 different disease conditions. Among members who responded to the calls, 52.9% were exposed to the original script and 47.1% to the new script. For the new script, 48.2% of the members accepted the offer to schedule the CMR, whereas 38.1% of members exposed to the original script accepted the service. Multivariate logistic regression was employed to examine factors that may influence the member’s decision on the CMR offer. Members who received the new script were 1.578 (95% CI = 1.45-1.72) times more likely to accept the CMR offer compared with those who received the original script. Among other factors, number of chronic medications (odds ratio [OR] = 1.038, 95% CI = 1.020-1.057), number of disease conditions (OR = 1.039, 95% CI = 1.014-1.064), and member’s previous involvement in the MTMP were positively associated with acceptance of CMR offer.

CONCLUSIONS: The new script outperformed the original script in promoting members’ acceptance to the CMR; yet, there continues to be room for improvement. The new script will be further improved based on the results from 2012, and the improved script is planned to be tested in 2013. Further, findings suggest that efforts should also be directed at members who do not respond to phone calls or mail offers to participate in CMR service.

SPONSORSHIP: This research was funded by Elsevier/Gold Standard, Tampa, FL.
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**BACKGROUND:** Copayment pricing has been shown to influence medication consumption behavior. Prior to 2010, patients paid a flat copayment of $8 per 30-day supply in the Department of Veterans Affairs (VA). However, some veterans during this period were exempt from copayments depending on a multitude of factors determining benefits.

**OBJECTIVE:** To evaluate the association between copayment status and adherence to statin therapy.

**METHODS:** A retrospective cohort study using data from the VA was performed to test the study objective. Data were extracted from the Veterans Integrated System Network 22, a region that includes sites at California (Los Angeles, Long Beach, San Diego, and Loma Linda) and Nevada (Las Vegas) and an enrollment of approximately 329,000 members. Patients were included if they were a new statin user between the periods of November 30, 2006, and December 2, 2007. Copayment status was categorized as (a) no copayment (NC), (b) copayment but non-service connected (NSC), and (c) copayment but service connected (SC). Medication copayment status for patients within the VA was determined by service connection status, which was awarded based on factors such as disability related to service, socioeconomic status, and military service.

Primary outcome was the medication possession ratio (MPR) at 12 months post-index date. Summary statistics were performed via 1-way ANOVA and Pearson chi-squared tests. Multiple linear regression was performed to evaluate the relationship between copayment status and adherence to statin medications for those that did not have a copayment.

**RESULTS:** Patients in the NSC group were older (65.5 years) compared with patients in the SC (62.6 years) and NC (61.2 years) groups (P < 0.001). Patients who did not pay a copayment had more medications on their profile at baseline (8.5 medications) compared with the SC (6.6) and NSC (6.7) groups (P < 0.001). There were more females in the NC group (n = 158) compared with the SC (N = 122) and NSC (n = 55) groups (P < 0.001). For the main outcome, patients without a statin copayment were associated with a 0.03 increase in MPR (P = 0.01) versus the SC reference group. Patients with a copayment that was NSC were associated with a 0.03 increase in MPR (P < 0.01) versus the SC reference group.

**CONCLUSIONS:** In this analysis, we found an improvement in adherence to statin medications for those that did not have a copayment.

**TABLE**

<table>
<thead>
<tr>
<th>Copayment Category</th>
<th>Increase in MPR</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Copayment (service connected group)</td>
<td>Reference</td>
<td>N/A</td>
</tr>
<tr>
<td>Zero copayment</td>
<td>0.03</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Copayment (nonservice connected)</td>
<td>0.01</td>
<td>0.10</td>
</tr>
</tbody>
</table>

MPR = medication possession ratio.

Additionally, our results revealed a nonsignificant increase in MPR with patients who had a copayment but were not service connected. Findings may differ in non-VA populations.

**SPONSORSHIP:** This research was conducted by Western University of Health Sciences College of Pharmacy, Pomona, CA, without external funding.

**Lack of Overall Dose Escalation Between 2007 and 2012 with Etanercept (Enbrel) and Adalimumab (Humira)**

Ganderson B, Johnson S, Gleason PP,* Starner CI. Prime Therapeutics LLC, 1305 Corporate Center Dr., Eagan, MN 55121; pgleason@primetherapeutics.com, 800.858.0723

**BACKGROUND:** Etanercept (Enbrel) and adalimumab (Humira) are tumor necrosis factor (TNF) blockers indicated for a variety of inflammatory autoimmune conditions (e.g., rheumatoid arthritis). In 2011, among Prime’s commercially insured customers, adalimumab and etanercept were the top 1 and 3 drugs by percentage of spend, respectively. Adalimumab 2011 per member per month (PMPM) was $1.50 (2.3% of overall) and etanercept PMPM was $1.43 (2.2% of overall). Drug costs in the autoimmune category have continued to rise over the past 5 years, and there is some literature to suggest adalimumab dose increases beyond labeling may be occurring.

**OBJECTIVE:** To assess dose and cost patterns of etanercept and adalimumab to identify potential opportunities for enhanced management.

**METHODS:** Pharmacy claims data from 9 million commercially insured members with Prime Therapeutics pharmacy benefit coverage were queried. All paid claims for etanercept and adalimumab were captured from January 1, 2007, through June 30, 2012. To evaluate dose changes between the 2 products, the average mg per day for all claims in the quarter was calculated starting on January 1, 2007. To permit comparisons between etanercept and adalimumab, which have different daily mg dosing guidelines, each drug’s average dose per day starting in Q1 2007 was normalized to 1. The subsequent average quarterly values of daily dose were compared with the standardized value from Q1 2007. Average quarterly gross cost per day for each product was calculated.
using total paid amounts on the pharmacy claim (health plan and member share). The compound annual growth rate (CAGR) was used to describe all trends from 2007 through 2012.

RESULTS: The average mg per day for etanercept in Q1 2007 was 8.068 and for adalimumab 3.479. Over 4.5 years, the average mg per day for each product slightly decreased to an average of 7.541 for etanercept and 3.256 for adalimumab in Q2 2012. The change in average mg per day between Q1 2007 and Q2 2012 was -13.6% and -3.0% for etanercept and adalimumab, respectively (Figure 1). Average daily gross costs for etanercept starting in Q1 2007 were $54.96 and increased to $76.00 in 2012, a 38.3% increase. Average daily gross costs for adalimumab increased 38.4% in Q1 2007 ($57.98) to $80.24 in Q2 2012. Since 2007, the wholesale acquisition cost (WAC) of etanercept has had a CAGR of 8.0%. Changes in WAC between 2011 and 2012 were more than 12.0%. Since 2007, adalimumab had seen similar WAC price increases with a CAGR of 7.8% and double digit price increases in 2011 (13.2%) and 2012 (11.1%; Figure 2).

CONCLUSIONS: The current findings do not support dose increases in the TNF blockers since 2007. In fact, it appears that on a mg per day basis, doses may actually be decreasing. WAC prices for etanercept and adalimumab have been steadily increasing and seem to be rising at a faster rate in more recent time periods. Increasing daily costs for each of these drugs has been primarily driven by manufacturer price increases.

SPONSORSHIP: This research was conducted by Prime Therapeutics LLC, Eagan, MN, without external funding.

Measuring Brand Drug Coupon Availability and Relative Consumer Behavior Incentives by Drug Class and PBM Plan Design

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RESULTS: The average mg per day for etanercept in Q1 2007 was 8.068 and for adalimumab 3.479. Over 4.5 years, the average mg per day for each product slightly decreased to an average of 7.541 for etanercept and 3.256 for adalimumab in Q2 2012. The change in average mg per day between Q1 2007 and Q2 2012 was -13.6% and -3.0% for etanercept and adalimumab, respectively (Figure 1). Average daily gross costs for etanercept starting in Q1 2007 were $54.96 and increased to $76.00 in 2012, a 38.3% increase. Average daily gross costs for adalimumab increased 38.4% in Q1 2007 ($57.98) to $80.24 in Q2 2012. Since 2007, the wholesale acquisition cost (WAC) of etanercept has had a CAGR of 8.0%. Changes in WAC between 2011 and 2012 were more than 12.0%. Since 2007, adalimumab had seen similar WAC price increases with a CAGR of 7.8% and double digit price increases in 2011 (13.2%) and 2012 (11.1%; Figure 2).

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SPONSORSHIP: This research was conducted by Prime Therapeutics LLC, Eagan, MN, without external funding.
BACKGROUND: Brand manufacturer coupons grew 264% in 2011; $10,000 per member per year limits are common. The weak economy, increases in generics and over the counters, new electronic marketing venues, and brand manufacturer’s legal mandate to fill the Medicare Part D donut hole all add to the urgency of a significant coupon strategy. Coupons allow brand cost increases to be passed to private plan payers rather than members and, in so doing, weaken pharmacy benefit management (PBM) plan designs used to incent adherence, lower cost drugs, and delivery channels.

OBJECTIVE: To clarify and quantify private PBM payer and member stakes given brand drug manufacturers’ coupon strategies.

METHODS: This research measures the percentage of brands offering coupons, their potential dollar value as a percentage of total and members’ brand costs, and generic alternative costs for 2 PBM clients. Client 1 has 2 coverages: a health reimbursement account (HRA) with 60% average member share and a 35% share plan. Client 2’s plan has 10% member share. Online brand coupon sites were checked in September 2012. Reliable information was matched against the claims from the 2 clients.

RESULTS: Brand coupon potential was 10.9% of total plan and 34.6% of brand member spend. Coupons were available in 52 (under 1%) drug classes, comprising 47.6% of cost. The average age of utilities of drug classes offering coupons was 53 years versus the 37-year all-utilizer average. For low member share plans, brand member costs can be negative (coupons can exceed copays). At 100% coupon redemption, average member retail brand costs would be less than mail for all 3 plans. For top coupon classes, coupons were 50%-67% of total cost and exceeded member cost for all 3 plans.

CONCLUSIONS: Because expected drug use and age are directly correlated, and coupons are targeted at classes used by higher-aged patients, private payers with high average ages will absorb the largest shift from the coupon strategy. Most coupon returns are maximized with shorter fills, directly counting generic and 90-day fill, cost, and adherence goals. Nonadherence causes 10% of hospitalizations and 75% of readmissions. Coupons are increasingly requiring otherwise confidential member info coveted for direct marketing. Coupon offers exceed member share for low member share plans, incenting perverse over- and misutilization. Comprehensive UM programs, including mandatory generics and mail, targeted member and doctor communication regarding coupons, plan design, health, and cost, are vital to curbing costs and increasing adherence.

SPONSORSHIP: This research was conducted by CVS Caremark, Northbrook, IL, without external funding.

Medicaid Pharmacy Benefit Carve-Ins and Their Impact on Generic Dispensing Rates and Program Costs

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BACKGROUND: Several state-run Medicaid programs are turning to traditional managed care organizations (MCOs) to manage their pharmacy benefit programs after previously carving out their pharmacy benefits to state-run fee-for-service programs. Pharmacy carve-ins arranged by MCOs are often associated with more complete monitoring of members’ prescription drugs, where high utilizers, inappropriate use, and candidates for disease and case management can be identified, thus, effectively addressing the ‘total person’ from a clinical and cost perspective. Previous research conducted by CVS Caremark showed a decrease in generic dispensing rates (GDR) and an increase in program costs associated with the movement to a carve-out arrangement. Recent legislative changes promoting carve-in arrangements gave us the opportunity to provide updated research that investigates what happens when a state moves in the opposite direction, from a carve-out to a carve-in arrangement. Preliminary findings from this updated research reaffirm the notion that traditional pharmacy benefit programs managed by an MCO lead to improved utilization and cost outcomes. Specifically, these recent CVS Caremark data show a significant increase in GDR and decrease in costs for state-run Medicaid programs that returned to a carve-in pharmacy benefit arrangement offered by traditional MCOs.

OBJECTIVE: To evaluate the impact on GDR and costs on previously state-run Medicaid programs after their pharmacy benefits were carved-in to a traditional MCO.

METHODS: This is a retrospective observational study design using claims post-implementation from an integrated database of administrative pharmacy claims to measure the impact on lower cost generic drug utilization when a state moves to a carve-in program. GDR and cost impacts were evaluated from data that included generic drug launches for a 12-month time period. Results are based on findings from several large Medicaid health plans previously operating state-run fee-for-service programs. T-test and/or ANOVA analyses were performed to determine the statistical significance of the results.

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RESULTS: GDR increased an average of 12%, and gross drug costs per member per month decreased 18% over the initial 11-month time period following implementation of the carve-in program for several Medicaid plans. Furthermore, controlling for generic drug launches yielded approximately a 10% increase in GDR and a 13% decrease in gross drug costs per member per month.

CONCLUSIONS: The findings from this study indicate that a pharmacy benefit design that encourages use of generic medications leads to an increase in GDR and thus a decrease in costs, even while controlling for generic drug launches. Carve-in approaches appear to be associated with positive utilization management and cost benefit. They allow for improved care coordination, since pharmacy and other medical benefits are managed under lcnty.

SPONSORSHIP: This research was conducted by CVS Caremark, Northbrook, IL, without external funding.

Medical Costs Associated with Treatment Failure with Over-the-Counter or Prescription Constipation Treatments in Patients with IBS-C in a Medicaid Population

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BACKGROUND: Pharmacologic treatments for irritable bowel syndrome with constipation (IBS-C), a common chronic functional gastrointestinal disorder characterized by recurrent symptoms of abdominal pain and/or discomfort and altered bowel function, include over-the-counter (OTC) laxatives, bulking agents, and stool softeners and prescription (Rx) medications.

OBJECTIVE: To estimate the incremental medical costs associated with indicators of treatment failure with OTC or Rx constipation treatments in IBS-C patients in a Medicaid population.

METHODS: This was a retrospective cohort study using de-identified medical and pharmacy claims from the Missouri Medicaid program (1997-2010) to assess health care resource utilization (HRU) and costs in IBS-C patients with versus without indicators of treatment failure while receiving constipation medications. Inclusion criteria were adult patients (age ≥ 18 years) who had ≥ 1 claim with a diagnosis of IBS (ICD-9-CM code 564.1x), ≥ 2 constipation-diagnosis claims (ICD-9-CM code 564.0x), and ≥ 1 constipation-treatment claim in ≤ 1 year of an IBS diagnosis. Exclusion criteria included having a diarrhea-diagnosis claim (ICD-9-CM code 564.5x) or antidiarrheal claim during the 6-month period before the index date, which was defined as the date of the first constipation-treatment claim initiated in ≤ 1 year of an IBS diagnosis. Patients were categorized into 2 subgroups based on the type of index treatment: OTC or Rx. In the subgroups, indicators of treatment failure, HRU, and costs were observed during the 1-year period following the index date. Indicators of treatment failure were defined as switch or addition of new constipation therapy; IBS- or constipation-related inpatient or emergency room admission; megacolon diagnosis; a constipation-related medical procedure; or use of colchicines, misoprostol, or rifaximin. HRU was defined as any claim for service and measured using incidence rate ratios (IRRs). Incremental HRU and health care costs (USD 2010; adjusted to USD 2011 values using the Consumer Price Index inflation rate), which were measured from a public payer perspective, were compared between study cohorts using multivariate generalized linear regression models with a log link and a negative binomial distribution for HRU (results reported as IRRs) and a gamma distribution for health care costs (reported as cost differences). Unadjusted P values were calculated using Wilcoxon rank-sum tests.

RESULTS: This analysis included 1,723 and 1,203 IBS-C patients with index claims for OTC and Rx medication, respectively, 49.4% and 41.6% of these, respectively, experienced ≥ 1 indicators of treatment failure. Demographic characteristics were similar for patients with or without indicators of treatment failure. In both subgroups, indicators of treatment failure were associated with more HRU, such as the number of inpatient days (OTC subgroup, adjusted IRR = 1.72; Rx subgroup, adjusted IRR = 1.87; both P < 0.001) and higher incremental medical costs (table).

CONCLUSIONS: Indicators of treatment failure with OTC or Rx constipation medications are associated with substantial incremental HRU and health care costs for IBS-C patients and payers.

SPONSORSHIP: This research was funded by Forest Laboratories, Inc., Jersey City, NJ, and Ironwood Pharmaceuticals, Inc., Cambridge, MA.

Medication Reconciliation in Community Pharmacy

Wurtz KA,* South Dakota State University College of Pharmacy, Box 489, Elk Point, SD 57025; kawurtz@jacks.sdstate.edu, 605.670.8105

BACKGROUND: Many hospitals have implemented medication reconciliation programs that consist of making the most accurate medication file for the patient. However, even with these programs the patients’ medication files continue to differ from the community pharmacy records. Theoretically, the implementation of community pharmacy-

<table>
<thead>
<tr>
<th>TABLE Medical Costs</th>
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</thead>
<tbody>
<tr>
<td>Cost Type</td>
</tr>
<tr>
<td>-----------</td>
</tr>
<tr>
<td>Patients with ≥1 Indicator of Treatment Failure (n = 851)</td>
</tr>
<tr>
<td>Hospital admissions</td>
</tr>
<tr>
<td>Outpatient visits</td>
</tr>
<tr>
<td>Emergency room visits</td>
</tr>
<tr>
<td>Total mean medical costs</td>
</tr>
</tbody>
</table>

Note: Costs are reported as mean (standard deviation) in 2011 dollars unless otherwise defined.

*Patients with index claims for OTC and Rx treatments were included in both subgroups.

Pc0.004 versus patients without indicators of treatment failure.

OTC = over the counter; Rx = prescription.
based programs could provide even greater patient safety than achieved with hospital programs. In addition, the community pharmacy-based medication reconciliation program can impact health care provision in various other settings such as nursing homes, primary care clinics, and assisted living. A collaborative team was formed between a pharmacy, a clinic, and an assisted living facility to explore the impact of a medication reconciliation program in a rural area.

**OBJECTIVE:** To measure the impact, satisfaction, and feasibility of a community pharmacy-based medication reconciliation program in a rural setting.

**METHODS:** The study was conducted in a rural community between June and August 2012. The program involved a community pharmacy, clinic, and assisted living facility. The program entailed the clinic or assisted living facility faxing the patient’s prescription list to the pharmacy, the pharmacist comparing the list to the pharmacy records (actual product procurement), and the pharmacist contacting the provider. A total of 106 patients’ medication regimens were examined (53 clinic patients, 6 assisted living facility patients). The feasibility and utility of the program was analyzed with an open-ended question survey given to the pharmacy staff and health care facilities involved.

**RESULTS:** A total of 101 discrepancies were found among 106 patients (mean 1.7, SD 1.6, range 0–7 discrepancies/patient). The majority of the discrepancies were found in clinic patients (93.1%, 94 discrepancies; 1.8 discrepancies/patient) with the remainder found in patients residing in the assisted living center (1 discrepancy/patient). Discrepancies comparing the provider profile to actual medication purchased included discontinued medications remaining on the provider profile (28%), current medications omitted from the provider record (25%), and wrong medication strength on the provider list (19%). Interventions resulted in updating medication profile (60%) and discontinuing medications (38%). A total of 17 people completed the feasibility and utility survey. The survey conducted following completion of the program found the average estimated time for the entire process was 5 minutes. Health care professionals involved in the study were extremely satisfied with the program and plan to continue using the process.

**CONCLUSIONS:** Medication reconciliation identified frequent inconsistencies that lead to medication discontinuation 40% of the time. Based on the amount of time required to complete the task, large impact, and high level of satisfaction, this program should be considered for use by community pharmacists.

**SPONSORSHIP:** This research was funded by Walmart-SDSU Summer Leader Fellowship Grant, Brookings, SD.

**Methods to Detect Adverse Drug Reactions Using Automated Health Care Databases**

Consaul JM, *Madison T, Regan TS. University of Florida College of Pharmacy, P.O. Box 100484, Gainesville, FL 32610; jconsaul1@ufl.edu, 352.476.4779

**BACKGROUND:** Automated health care databases, such as health insurance claims databases, are sometimes used to conduct active surveillance for adverse drug reactions and to investigate safety signals. Health insurance claims databases provide large sample sizes, which are essential to identify rare outcomes and to provide information on adverse drug reactions in real-world populations. Legislation introduced through the Food and Drug Administration Amendments Act of 2007 resulted in the development of a national system called the FDA Sentinel System to conduct surveillance for adverse drug reactions using automated health care databases. The initial phases of FDA’s Sentinel System have focused on methods to identify serious adverse drug reactions associated with medication use, including some of the designated medical events (DMEs), a list published by the FDA in 2003 of adverse outcomes correlated with medication use that have a high risk of severe morbidity or mortality. A frequently used method is to develop algorithms using ICD-9-CM diagnosis codes to search health insurance claims data for adverse drug reactions. The performance of these algorithms is measured by conducting patient chart reviews to confirm outcomes to establish the reliability of algorithm use alone.

**OBJECTIVE:** To identify and characterize methodological work completed to date on algorithms used to identify DMEs in health care databases and compile a library of adverse drug reaction search algorithms that could be used by managed care organizations in their own patient populations.

**METHODS:** A literature review was conducted using a subset of the FDA’s proposed DMEs. Included articles were published within the last 10 years, had data only from North American patients, and included MeSH subheadings for “epidemiology,” “drug effects,” or “chemically induced.” In addition, the websites for the FDA Mini Sentinel Pilot Program and the Observational Medical Outcomes Partnership (OMOP) website were investigated for additional studies.

**RESULTS:** Ten systematic reviews were found that investigated methods used to identify 10 of the 16 DMEs that we selected. These reviews covered the following DMEs: toxic epidermal necrolysis, seizure disorders, Torsades de pointe, ventricular fibrillation, acute liver failure, acute kidney failure, anaphylaxis, lung fibrosis, aplastic anemia, and acute respiratory failure. Since a principle measure of validity for search algorithms is positive predictive value (PPV), we defined search algorithms with a PPV threshold of ≥70% as a plausible method for researchers to use in conducting active surveillance or signal investigation of a specific DME. DMEs with search algorithms with PPVs <70% were deemed areas of opportunity for further research. For the 10 DMEs found, only 3 had algorithms identified that met the PPV threshold of ≥70%; the remaining 7 had algorithms with PPVs ranging from 0%-51%. Limitations of this study included the restriction of our search to PubMed, the FDA Mini Sentinel website, and the OMOP website, which may have excluded published work.

**CONCLUSIONS:** Opportunity exists for further algorithm development in low performance and understudied DMEs. Algorithms that exceeded 70% PPV for DMEs may provide an opportunity for managed care-based researchers to reliably identify and characterize adverse drug reactions in their respective patient populations with the ultimate goal to improve patient outcomes.

**SPONSORSHIP:** This research was conducted by University of Florida College of Pharmacy, Gainesville, FL, and Xcenda, Palm Harbor, FL, without external funding.

**Methods to Detect Adverse Drug Reactions Using Health Care Databases**

Consaul JM, *Madison T, Regan TS. University of Florida College of Pharmacy, P.O. Box 100484, Gainesville, FL 32610; jconsaul1@ufl.edu, 352.476.4779

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**SPONSORSHIP:** This research was funded by Walmart-SDSU Summer Leader Fellowship Grant, Brookings, SD.
information to make formulary decisions regarding the correspond-
ing therapeutic products. This survey assesses the current landscape
in acquiring information about diagnostics from drug and diagnostic
manufacturers.

OBJECTIVE: To characterize how drug and diagnostic manufacturers
respond to unsolicited information requests about FDA approved, com-
mercially available diagnostic tests.

METHODS: Five oncology biomarkers were selected for this study: 
ALK, BRAF V600E, EGFR, HER2, and KRAS. Information on the
FDA-approved tests, the drugs, and their manufacturers were collected.
Various resources, including the Summary of Safety and Efficacy Data
(SSED), product websites, and drug labels, were used. Each drug and
diagnostic manufacturer was called via telephone from the perspective
of a clinical pharmacist requesting information about a particular diag-
nostic test to assist in formulary decision making about the correspond-
ing drug. Specifically, information about the test’s analytical validity,
clinical validity, and clinical utility was asked.

RESULTS: A total of 20 calls were made to manufacturers (7 diagnostic
and 13 drug manufacturers). 38% of requests to drug manufacturers
resulted in a medical letter containing little or no information requested
about the diagnostic test, while 23% of requests resulted in a referral to
the diagnostic test manufacturer. An additional 23% resulted in both
outcomes, with the remaining 15% of requests resulting in referrals
to company websites. On the other hand, 71% of calls to diagnostic
manufacturers resulted in referrals to company websites where package
inserts for tests were found 60% of the time. Only 14% of information
requests from diagnostic manufacturers resulted in the provision of the
package insert for the test.

CONCLUSIONS: While diagnostic manufacturers responded via techni-
cal service departments staffed mainly by nonhealth care professionals,
drug manufacturers responded via medical information departments
staffed by health care professionals. Astonishingly, only 25% of calls
resulted in access to some or most of the information requested about
diagnostic tests. This study shows that limitations exist in obtaining
information about FDA-approved diagnostic tests from diagnostic and
drug manufacturers. It may be interesting to evaluate the provision of
diagnostic test information in the future following adoption of the
AMCP addendum on companion diagnostic tests.

SPONSORSHIP: This research was conducted by Genentech, South San
Francisco, CA, without external funding.

One State Medicaid’s Strategy to Overcome Limitations to a
Prescription Drug Cap Policy Using a 90-Day Maintenance List

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BACKGROUND: In July 2005, a legislative action required that the
Mississippi Division of Medicaid (DOM) institute a prescription benefit
cap to limit the total number of prescriptions a beneficiary could receive
each month to 5 (maximum of 2 brand name) for non-long-term care
beneficiaries utilizing the fee-for-service (FFS) prescription benefit.
An exemption to the benefit limit was allowed for beneficiaries under the age
of 21 after medical necessity for additional prescriptions had been deter-
mined. At the same time as the prescription benefit limit change, the
DOM released a list of medications that could be prescribed in 90-day
increments to allow for more prescription fills (i.e., the 90-day fill would
only count for 1 prescription “slot” in month 1, freeing up a prescription
“slot” in months 2 and 3). The 90-day maintenance list has been updated
several times since 2005, with the latest revision on April 1, 2012.

OBJECTIVE: To (a) determine the extent of 90-day maintenance list
adoption among prescribers, in particular with beneficiaries consistently
reaching the monthly benefit limit of 5 prescriptions at least 5 out of
the 6-month study period, and (b) to describe the patient population
reaching the prescription benefit limit, including demographics, pre-
scribers, and health conditions.

METHODS: The target sample was identified as beneficiaries reach-
ing the prescription benefit limit at least 5 times during the 6-month
study period. Beneficiaries classified as long-term care recipients and
Medicare dual eligibles were excluded from the analysis due to differ-
ences in monthly prescription benefit limits compared with the rest of
the Medicaid population. Prescribers were classified as adopters
or nonadopters based on whether they prescribed 90-day supplies of
medicines included on the 90-day maintenance list to any Medicaid FFS

RESULTS: After excluding long-term care recipients and Medicare dual
eligibles, prescription claims were found for a total of 117,977 unique
beneficiaries and 11,762 unique prescribers during the study period,
representing 362,102 patient-months and 946,881 prescription records.
A total of 30,913 (26.20%) beneficiaries reached the prescription benefit
limit at least 1 month, with 3,518 (2.98%) beneficiaries reaching the limit
≥5 months during the 6-month study period. Of the prescribers
with beneficiaries consistently reaching the prescription benefit limit
(n = 4,665), only 317 (6.80%) had written a 90-day prescription for
those beneficiaries. Surprisingly, there were 2,265 prescribers who had
adopted 90-day maintenance prescribing for beneficiaries not reaching
the prescription limit but had failed to do so in the beneficiaries consis-
tently reaching the prescription limit.

CONCLUSIONS: Beneficiaries consistently reaching the monthly ben-
efit limit would most benefit from receiving a 90-day prescription of a
maintenance medication. While the 90-day maintenance list has helped
some beneficiaries receive more monthly medications, the relatively low
number of prescribers utilizing the 90-day maintenance list indicates a
need for educational outreach to encourage utilization of the list, par-
ticularly to those prescribers who have beneficiaries in greatest need
of additional prescriptions. Based on this baseline analysis, a follow-up
intervention study is underway that seeks to determine the extent of
maintenance list adoption following a targeted educational initiative.

SPONSORSHIP: This research was conducted by the University of
Mississippi, University, MS, without external funding.

Outcomes of an Interactive Medication Therapy Management
Program: Comprehensive Medication Review Completion Rates,
Recommendation Acceptance Rates, and Return on Investment

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BACKGROUND: Medication therapy management (MTM) has been
heavily discussed since its introduction in the Medicare Modernization
Act of 2003 but has been slow growing with limited outcome data.
With the release of the 2013 Center for Medicare and Medicaid Services
(CMS) requirements for MTM programs, there is now room for MTM to
take center stage with its inclusion into CMS's Display Measures, with
the proposal to be moved to the Star Ratings system for 2014. According
to CMS, MTM is a patient-centric and comprehensive approach to
improve medication use, reduce risk of adverse events, and improve
collection adherences. Comprehensive Medication Reviews (CMR) are

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the standard of care designated by CMS, with national average completion rates of less than 10%. In order to ensure CMS compliance, health plans are now seeking more definitive outcomes data to improve quality and provide savings opportunities.

**OBJECTIVE:** To demonstrate outcomes, patient savings, and returns on investment recognized from an interactive MTM program of a large national health plan.

**METHODS:** We analyzed a group of 2,893 patients who were eligible for a CMR during 2011. Eligible patients were contacted via telephone by a pharmacist/student pharmacist team. Results of the CMR, including pharmacist recommendations, were mailed to the patient and provider. Recommendation acceptance rates were calculated by comparing recommendations made during the CMR to prescription claims data. Direct drug expenditure (DDE) savings were calculated from 2 time periods: January through December 2010 and January through December 2011. Patients who were MTM-eligible were stratified into an intervention group (CMR completed) or control group (CMR not completed). Differences in DDE were assessed for 2 time periods using student t-tests. Return on investment (ROI) was calculated using prescription claims and service billing invoice data from a large health plan.

**RESULTS:** The CMR completion rate for MTM eligibles in 2011 was 38.1% (n=1,103). When contacted by telephone, approximately 90% of patients opted to participate in the CMR. The acceptance rate of recommendations identified during the CMR was 82.6% (74.2% excluding vaccination recommendations). Common recommendations included needs additional drug therapy, incorrect administration, dosage too low/ high, adverse drug reaction, and brand-to-generic switch. Average annual DDE savings was $1,192 for MTM eligibles who received a CMR compared with those who did not (P=0.001). Baseline DDE for 2010 was similar in both the intervention and control groups (P=0.06). Total annual ROI was 7.1% for 2011.

**CONCLUSIONS:** Telephonic MTM services using a pharmacist/student pharmacist model provides significant savings and ROI in patients who received a CMR compared with those who did not. A potential limitation to the study is that the health plan switched its pharmacy benefit management company in 2011; however, this variable was accounted for using the control group compared with baseline DDE in 2010. Annual trends in drug cost increases were not accounted for. Medical claims were not analyzed in this study; however, their inclusion into outcomes data will be the next step in MTM value research.

**SPONSORSHIP:** This research was conducted by VRx Pharmacy Services, LLC, Salt Lake City, UT, without external funding.

### Out-of-Pocket Costs and Prescription Reversals:
The Case of Oral Linezolid

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**BACKGROUND:** Linezolid is indicated in the treatment of vancomycin-resistant Enterococcus faecium infections, complicated and uncomplicated skin and soft tissue infections (SSTI), and nosocomial and community-acquired pneumonia. Among antibiotics used to treat SSTI and pneumonia, linezolid is available in both intravenous and oral forms. This availability of intravenous and oral forms may allow for a shortened hospital stay if treatment is continued orally post-discharge, resulting in lower total costs of treating the infection. However, copay may distort benefit design for oral linezolid generally results in higher patient out-of-pocket costs (compared with copay), which is associated with prescription reversals and subsequent treatment with alternative antibiotics or in some cases no antibiotic treatment altogether. If patients who reverse their prescriptions for oral linezolid have higher medical and total health care costs as a consequence of their reversals versus patients who filled their prescriptions for oral linezolid, then payers would be advised to improve patient access to this important medication.

**OBJECTIVE:** To (a) determine the relationship between benefit design, out-of-pocket costs, and prescription reversals among Medicare members prescribed oral linezolid, post-discharge from a hospital stay for an SSTI or pneumonia, and (b) investigate the impact of reversals on rehospitalizations and total health care costs among these patients.

**METHODS:** Medicare members from a national health plan prescribed oral linezolid post-hospitalization for SSTI or pneumonia were followed retrospectively. Members were identified by an oral linezolid prescription, June 1, 2007, to April 30, 2011, where the index event was a prescription fill or reversal ≤2 days before or ≥10 days after discharge from a hospitalization for SSTI or pneumonia. The association between out-of-pocket costs and reversal, and between reversal and rehospitalization 30 days post-index, were compared for members with a prescription fill versus reversal. A generalized linear model calculated adjusted total health care costs per member controlling for age, gender, geographic region, and clinical characteristics.

**RESULTS:** A final sample of 1,062 Medicare members was available for analysis. 16.5% of members reversed their prescriptions for oral linezolid. Demographic and clinical characteristics by fill versus reversal groups indicated there were no statistical differences in age, gender, or geographic region. However, a higher percentage of members filling their linezolid prescriptions had low income subsidy/dual eligibility status compared with members reversing their linezolid prescriptions (P<0.001). Mean out-of-pocket costs were higher for members with coinsurance ($46.52) versus copay ($7.05) plans (P<0.001), and reversal rates rose progressively from 2% for members with out-of-pocket costs of $0 to 27% for members with out-of-pocket costs >$100 (P<0.001). Infection-related rehospitalizations were 23% versus 9% for members with a prescription reversal versus fill (P<0.001). While post-discharge prescription drug costs were $1,229 lower (P<0.001), adjusted mean medical costs were $2,062 higher (P=0.003), and total health care costs were $1,281 higher (P=0.035) for reversal versus fill members.

**CONCLUSIONS:** Higher out-of-pocket costs and coinsurance rather than copay were associated with higher rates of reversal, and reversals were associated with higher rates of rehospitalization and adjusted total health care costs among Medicare members prescribed oral linezolid post-hospitalization for SSTI or pneumonia.

**SPONSORSHIP:** This research was funded by Humana, Inc., Louisville, KY, and Pfizer Inc., New York, NY.

### Outpatient Treatment and Clinical Characteristics of Patients with Aspergillus in the United States

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**BACKGROUND:** Aspergillus has many clinical manifestations, which may lead to changing treatment patterns.

**OBJECTIVE:** To evaluate new treatment patterns and clinical characteristics of U.S. patients diagnosed with aspergillosis within a large, commercially insured population.

**METHODS:** Adults aged ≥18 years with at least 1 inpatient admission, emergency room, or outpatient visit with an aspergillosis diagnosis (ICD-9-CM 117.3 or 484.6) between July 1, 2004, and March 2, 2011,
were identified retrovistically from the MarketScan databases. Patients with an aspergillosis diagnosis in the pre-index period were excluded. All patients were required to have at least 6 months of continuous pre-index and at least 1 month of continuous post-index health plan and pharmacy benefit enrollment. Clinical characteristics were summarized, and outpatient antifungal therapy in the post-index period was evaluated.

RESULTS: 5,499 patients with aspergillosis, with or without pneumonia, were identified. The mean age was 37.8 years; 48.6% were female; 30.1% had cancer; and 33.6% had an index diagnosis in the inpatient setting. Initial outpatient therapy included voriconazole (1,089, 19.8%), posaconazole (31, 0.09%), itraconazole (411, 7.5%), amphotericin B (83, 1.5%), echinocandin (132, 2.4%), more than 1 antifungal (23, 0.4%), and no therapy observed within 30 days of the index diagnosis (3,710, 67.5%). The mean duration of first observed antifungal therapy in days was 60.6 ± SD 91.1 for voriconazole, significantly longer than amphotericin B (19.6 ± 37.4, P < 0.0001), echinocandin (4.5 ± 12.9, P < 0.0001), and > 1 antifungal (2.2 ± 3.7, P = 0.0022). Mean days of first observed antifungal therapy was similar for posaconazole (47.1 ± 51.0) and itraconazole (53.6 ± 63.3) when compared with voriconazole. For those receiving voriconazole, 52.4% had their index diagnosis in the inpatient setting and 47.6% in the outpatient setting. Occurrence of index aspergillosis diagnosis in the inpatient setting was similar for those initially treated with voriconazole (52.4%) and > 1 antifungal (60.9%) when compared with voriconazole. However, significant differences (all P < 0.001) were noted with itraconazole (30.2%), amphotericin B (32.5%), echinocandin (34.1%), and no antifungal therapy within 30 days of index (28.9%). The pre-index mean Deyo Charlson Comorbidity Index (CCI) score was 2.7 ± SD 2.5 for voriconazole, which was significantly different from the CCI scores of patients initially treated with itraconazole and those receiving no antifungal therapy within the first 30 days of index (1.6 and 1.8, respectively, P < 0.0001). Pulmonary disease and immunocompromising conditions were commonly observed, especially cancer, neutropenia, and diabetes.

CONCLUSIONS: Substantial variation in outpatient antifungal therapy and clinical characteristics was observed. Combination therapy in the outpatient setting was uncommon, and most patients had no outpatient prescription claims for antifungals within the first 30 days. For those receiving therapy, voriconazole was most commonly administered, with a duration of initial treatment of about 2 months. Patients receiving voriconazole, posaconazole, amphotericin B, echinocandins, or > 1 antifungal had higher pre-index CCI scores compared with those receiving itraconazole or no antifungal therapy. Immunoconstricting conditions and pulmonary disease were very common. Additional studies are warranted to improve the understanding of treatment patterns and clinical characteristics of patients diagnosed with aspergillosis, especially regarding differences in outpatient versus inpatient care.

SPONSORSHIP: This research was funded by Astellas Pharma US, Inc., Northbrook, IL.

### Period and Point Prevalence and Incidence Rate of New Use of Biologic Anti-Inflammatory Agents Among 2.6 Million Commercial Members Continuously Insured for 3 Years

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BACKGROUND: A growing number of biologic anti-inflammatory (BAI) agents provide therapeutic alternatives within the same set of autoimmune diseases and are important drivers of health care cost. Health insurers need an understanding of BAI utilization patterns in order to assess management opportunities.

OBJECTIVE: To estimate (a) the number of members with diagnoses approved for treatment with a BAI, (b) the fraction with these diagnoses treated using 1 or more of these drugs, (c) the number and percentage who are new users of BAI therapy in a defined time interval, and (d) the distribution of new users by specific BAI.

METHODS: Integrated pharmacy and medical claims data from 2.6 million commercially insured members younger than 65 years on December 31, 2011, who were continuously enrolled from 2009 through 2011 were analyzed to determine prevalence of diagnoses and use of BAI. Diagnosis was assigned as Rheumatoid Arthritis (RA), Psoriasis, Crohn's disease, Ulcerative Colitis (UC), Ankylosing Spondylitis (Ank), or Juvenile Idiopathic Arthritis (JIA). Members had ≥3 medical claims with the respective ICD-9-CM diagnosis codes. BAI were defined as abatacept, adalimumab, alefacept, anakinra, certolizumab pegol, efalizumab, etanercept, golimumab, infliximab, tocilizumab, and ustekinumab or rituximab with RA diagnosis code. Point prevalence of BAI use on December 31, 2009, and December 31, 2011, was defined as a BAI pharmacy claim providing a supply within 60 days of a BAI medical claim providing a supply within 60 days of the BAI's standard medical

### TABLE

<table>
<thead>
<tr>
<th>Diagnosis prevalence during 2009 to 2011</th>
<th>RA</th>
<th>Psoriasis</th>
<th>Crohn's Disease</th>
<th>UC</th>
<th>Ank</th>
<th>JIA</th>
<th>Un-assigned</th>
<th>Any</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence of any BAI therapy during 2009 to 2011</td>
<td>1741</td>
<td>1190</td>
<td>561</td>
<td>154</td>
<td>22.3</td>
<td>4.6</td>
<td>16.6</td>
<td>410.2</td>
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<tr>
<td>Percentage with diagnosis treated with any BAI during 2009 to 2011 (%)</td>
<td>38.3</td>
<td>20.1</td>
<td>25.5</td>
<td>6.5</td>
<td>59.1</td>
<td>36.3</td>
<td>36.3</td>
<td>27.0</td>
</tr>
<tr>
<td>Point prevalence of BAI therapy on December 31, 2009</td>
<td>106.1</td>
<td>70.6</td>
<td>33.5</td>
<td>7.3</td>
<td>13.3</td>
<td>3.7</td>
<td>7.6</td>
<td>248.1</td>
</tr>
<tr>
<td>Point prevalence of BAI therapy on December 31, 2011</td>
<td>130.9</td>
<td>89.8</td>
<td>42.6</td>
<td>11.1</td>
<td>17.0</td>
<td>4.9</td>
<td>10.4</td>
<td>312.8</td>
</tr>
<tr>
<td>Increase in point prevalence, December 31, 2009, to December 31, 2011 (%)</td>
<td>29.0</td>
<td>27.2</td>
<td>27.2</td>
<td>56.6</td>
<td>27.8</td>
<td>34.2</td>
<td>377</td>
<td>29.4</td>
</tr>
<tr>
<td>Members on BAI therapy on both December 31, 2009, and December 31, 2011</td>
<td>87.1</td>
<td>55.3</td>
<td>26.1</td>
<td>5.4</td>
<td>10.6</td>
<td>2.9</td>
<td>5.0</td>
<td>192.7</td>
</tr>
<tr>
<td>New BAI users whose first BAI claim since January 1, 2009, was between January 1, 2010, and December 31, 2011</td>
<td>53.5</td>
<td>34.8</td>
<td>19.2</td>
<td>7.3</td>
<td>7.3</td>
<td>2.2</td>
<td>7.2</td>
<td>131.5</td>
</tr>
</tbody>
</table>

Ank = ankylosing spondylitis; BAI = biologic anti-inflammatory agent (abatacept, adalimumab, alefacept, anakinra, certolizumab pegol, efalizumab, etanercept, golimumab, infliximab, tocilizumab, and ustekinumab or rituximab if claim has diagnosis code for RA); JIA = juvenile idiopathic arthritis; N/A = not applicable; Psoriasis = psoriasis or psoriatic arthritis; RA = rheumatoid arthritis; UC = ulcerative colitis; Un-assigned = BAI cases that were not assigned a diagnosis.
Prescriber Interventions Targeting Gaps-in-Care for Persons with Diabetes Yield Measurable Medical Cost Savings

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BACKGROUND: In an effort to improve appropriate treatment of people with diabetes, a prescriber intervention program was deployed in a state government account with approximately 150,000 members. The population, composed of state and public school employees, includes both retirees and dependents. A real-time predictive risk score calculated during pharmacy benefit management (PBM) adjudication was used to refine targeting of prescribers for interventions designed to improve compliance with recommended diabetes therapy guidelines.

OBJECTIVE: To document actual medical savings over time for members whose prescribers received highly targeted letter interventions originating from a PBM.

METHODS: A matched case control evaluation was designed and executed comparing medical costs of an intervention (case) group to the control group. Medical data reflecting allowed amount paid for both the intervention group and the control group were used. These data were provided by the respective payers in the form of medical claim extracts. The “Intent to Treat” (ITT) population (i.e., intervention or case group) was defined as those diabetic patients whose prescriber received a statin or angiotensin-converting enzyme inhibitors (ACE)/angiotensin receptor blockers (ARB) guideline compliance letter in the last quarter of 2010. Prescribers letters were generated for diabetic patients who were lacking statin or ACE/ARB therapy in their drug histories. The matched observational cohorts (i.e., control group) were prescribers eligible for the same intervention during the same time period but lacking such interventions. Matched control cohorts belonged to a separate employer group that elected not to have prescriber interventions during this period. The evaluation baseline was 2010, and the evaluation follow-up period was 2011.

RESULTS: After matching at the baseline by demographics, comorbidities, and diabetic medication adherence, 1,169 cases and controls, respectively, were selected for the statin letter cohort, and 1,040 cases and controls, respectively, were selected for the ACE/ARB letter cohort. Stratification of cases by predictive risk score facilitated successful interventions with prescribers and produced measurable savings adjusted by control in the medical plan allowed amount exceeding $42 per pation per month (PMPM) for statin letters and $23 PMPM for ACE/ARB letters in the intervention population. Estimated savings in total allowed amount for the payer based on these measures exceeded $3,000,000 for the 2011 plan year and translated to an estimated $1.71 PMPM in medical cost savings across the eligible population.

CONCLUSIONS: This study is important to the practice of managed care pharmacy for several reasons. First, it measures the impact on medical costs and demonstrates the value of pharmacy care interventions and the use of pharmaceuticals on overall health care costs. Second, it demonstrates the value of using predictive risk scores, a new and valuable tool for pharmacy management. Finally, this study proves that clinical outcomes for people with diabetes, a growing concern in the United States, can be positively impacted through properly designed intervention programs. Use of predictive risk scores to refine targeting of prescribers results in effective interventions and measurable reductions in medical costs. Furthermore, predictive risk scores are valuable adjuncts for stratifying clinical intervention targets and should be considered for use by pharmaceutical care teams.

Prescription Savings Club Membership and Drug Utilization Behavior

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BACKGROUND: In one of four American adults lack adequate prescription drug insurance coverage, which can lead to high out-of-pocket expense and poor adherence. A Prescription Savings Club (PSC) program sponsored by a national pharmacy chain can help these patients by offering generic and brand prescription drugs at a discounted rate.

OBJECTIVE: To examine the utilization behavior of PSC and non-PSC members taking the most common chronic prescription drug classes and determining if they differ on generic utilization and medication adherence.

METHODS: This was a retrospective observational study based on 2011 pharmacy data from a national pharmacy chain. Patients utilizing medications in any of the following conditions or therapeutic/drug classes (diabetes, hyperlipidemia, proton pump inhibitors [PPI], beta-blockers, and nonselective calcium channel blockers) were identified and placed into 1 of the 3 payment segments: (1) exclusively cash payers (n=59,614), and (3) exclusively third-party administrator members (TPA; n=1,32,697). Medication adherence as measured by proportion of days covered (PDC) was compared by drug class and member segment after risk adjustment for age, gender, average household income, and number of unique therapeutic classes.

RESULTS: Patients in the PSC segment were much less likely to fill prescriptions for brand drugs than those in the TPA segment. Among diabetes patients, only 2.8% of the PSC segment, compared with 26.5% of the TPA segment, filled prescriptions for brand drugs. Among hyperlipidemia patients, 8.8% of the PSC segment, compared to 23.8% of the TPA segment, filled prescriptions for brand drugs. Compared with the cash segment, patients in the PSC segment were much more adherent.
The average risk-adjusted PDC for the PSC segment was 16.9% higher than the cash segment (71% vs. 55%; P < 0.001). Compared with TPA, the PSC segment tended to be more adherent to drug classes that had relatively low out-of-pocket costs (< $0.60/day) and less adherent to drug classes with higher out-of-pocket costs. In drug classes characterized with relatively low out-of-pocket costs, the average risk-adjusted PDC was 6% higher for the PSC segment than for the TPA segment (76% vs. 70%; P < 0.01). Conversely, the average risk-adjusted PDC in PPI was 13% lower for the PSC segment than for the TPA segment (52% vs. 65%) and the average risk-adjusted PDC in ibuprofen derivatives was 6% lower for the PSC segment than for the TPA segment (64% vs. 70%). In both cases, the difference was statistically significant (P < 0.01), and the drug classes had relatively high out-of-pocket costs.

CONCLUSIONS: PSC members appeared to be more cost conscious with their prescription drugs as they favored generic medications with low out-of-pocket costs. When compared with the TPA segment, PSC members tended to be more adherent in drug classes that have a relatively low out-of-pocket costs and less adherent in drug classes with higher out-of-pocket costs. By promoting generic medication utilization and offering discounts, the PSC program helped reduce patients’ out-of-pocket costs and improved their medication adherence.

SPONSORSHIP: This research was conducted by Walgreen Co., Deerfield, Ill., without external funding.

Reducing Drug Diversion in North Carolina: Medicaid’s Lock-In Program

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BACKGROUND: The Code of Federal Regulations (CFR) establishes a rule that allows Medicaid agencies to administer lock-in programs for recipients who overutilize prescription drugs. According to the most recent Medicaid Drug Utilization Review Annual Reports submitted by each agency, approximately 90% of states use lock-in programs to identify potential fraud or abuse of controlled drugs. In October 2010, North Carolina Department of Health and Human Services (DHHS) implemented a lock-in program. The program identified members who received multiple prescriptions for opiates and antianxiety medications. These members received clinical review and lock-in consideration.

OBJECTIVE: To determine the impact of North Carolina Medicaid’s lock-in program on pharmacy and medical services utilization and costs.

METHODS: Medicaid members with a history of more than 6 claims for opiate medications, more than 6 claims for benzodiazepine/antianxiety medications, or prescriptions for opiates and/or benzodiazepine/antianxiety medications from more than 3 prescribers in the most recent 2-month period were evaluated by a clinical pharmacist for lock-in. Based on the clinical review, members were recommended for lock-in to a single pharmacy and physician in the pharmacy claims processing system and Medicaid Management Information System (MMIS). Pharmacy and medical (i.e., inpatient, emergency department, and dental services) utilization trends and costs were evaluated for 6 months before and after lock-in among the targeted and comparison groups. The comparison group qualified for the lock-in program but was not selected for lock-in during the 12-month observation period.

RESULTS: One hundred and five members were locked in during November 2010. The number of opiate and benzodiazepine/antianxiety prescriptions in the lock-in group decreased from 2,728 to 6 months prior to lock-in to 1,207 after lock-in compared with an increase of 1,502 to 1,766 in the comparison group. Decreased use was also seen with other medications, such as anticonvulsants, NSAIDs, and skeletal muscle relaxants, while antidepressant use increased. Overall, the total amount paid for medications decreased by 10% in the targeted group compared with an increase of 27% in the comparison group. Medical utilization totals decreased 44% in the target group and increased 15% in the comparison groups, while costs decreased 51% and 39%, respectively. Overall, costs decreased $392,481 (39%) in the target group compared with $175,120 (28%) in the control group.

CONCLUSIONS: The North Carolina Division of Medical Assistance’s lock-in program decreased pharmacy and medical utilization and associated costs.

SPONSORSHIP: This research was conducted by Xerox State Healthcare, LLC, Richmond, VA, without external funding.

Retrospective Evaluation of a Long-Acting Insulin Switch on Hemoglobin A1c: Glargine to Detemir (RELISH)

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BACKGROUND: In 2011, Kaiser Permanente Redwood City (RWC) conducted a pilot study to convert type 2 diabetes patients using insulin glargine to insulin detemir. Previous randomized parallel-group studies in patients with type 2 diabetes have shown that there was no significant difference in mean hemoglobin A1c (HbA1c) between patients treated with glargine and detemir. There are very few studies of therapeutic interchanges from insulin glargine and detemir within the same patient group.

OBJECTIVE: To evaluate the clinical impact of a therapeutic interchange from insulin glargine to insulin detemir in type 2 diabetes patients at Kaiser Permanente Redwood City.

METHODS: The Retrospective Evaluation of a Long-Acting Insulin Switch on Hemoglobin A1c: Glargine to Detemir (RELISH) was a retrospective, single arm, observational study. Retrospective chart reviews were conducted on patients who participated in the glargine-to-detemir conversion to determine eligibility for the study based on the inclusion and exclusion criteria. The primary endpoints included HbA1c at 3-6 months after the glargine-to-detemir conversion, the change in HbA1c from baseline to the end of the study, proportion of patients with HbA1c < 7% and ≥ 7% at baseline and after the conversion, and the proportion of patients who continued on the new insulin detemir regimen versus flipped back to insulin glargine, and the documented reasons for flipping back to insulin glargine. Secondary endpoints included diabetes-related emergency department visits and reported hypoglycemia episodes within the first 4 months after insulin detemir prescription pickup. A two-tailed Student t-test with a significance level of 0.05 and a confidence level of 95% was conducted to determine if there was a significant difference in the change in HbA1c from baseline after the conversion. Subgroup analysis was performed for patients not enrolled in a PharmD/RN diabetes care management program (CM).

RESULTS: Sixty-two patients qualified for the study based on inclusion and exclusion criteria. In all patients with available baseline and post-conversion HbA1c data (n = 41), the mean baseline HbA1c changed (HbA1c 8.1% [SD 1.3] vs. HbA1c 8.4% [SD 1.6]), respectively, with mean change in HbA1c of 0.2% [SD 0.7]; P > 0.01. After exclusion of patients in CM (n = 34), there was no difference in mean HbA1c pre- and post-conversion (HbA1c 7.9% [SD 1.4] vs. HbA1c of 8.0% [SD 1.7]), respectively, with mean change HbA1c 0.2% [SD 0.7]; P > 0.01. There was no change in the proportion of patients with HbA1c < 7% from baseline to post-conversion in either group. Nine patients (14.5%) flipped back to insulin glargine after successful conversion to detemir. Within 4 months

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after conversion, 9 patients reported hypoglycemic events, and 1 patient had a diabetes-related emergency department visit.

CONCLUSIONS: The change in mean HbA1c after conversion from insulin glargine to insulin detemir suggests that diabetes control may have been affected by the switch. However, there were confounding factors (such as CM) that may have affected these results. After excluding the CM patients, we found that converting insulin glargine to insulin detemir provided similar blood sugar control with no changes in mean HbA1c. In patients that do not require the additional intensive management, a therapeutic interchange from insulin glargine to insulin detemir results in similar blood sugar control.

SPONSORSHIP: This research was conducted by Kaiser Permanente, Redwood City, CA, without external funding.

■ Retrospective Study of Persistence and Health Care Charges Among Opioid-Dependent Patients Treated with Buprenorphine/Naloxone Film and Tablet Formulations Using a Privately Insured Retrospective Database

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BACKGROUND: The buprenorphine/naloxone combination (BUP/NAL) has been available in a film formulation since 2010 for the treatment of opioid dependence. A clinical trial showed that patients preferred the film to tablet formulation.

OBJECTIVE: To analyze insurance claims data comparing patient persistence and health care charges between film and tablet BUP/NAL formulations.

METHODS: Retrospective cohort analysis was performed using medical claim records extracted from the Invision DataMart database. Patients initiating treatment with BUP/NAL after the launch of film (September 2010) were classified into 2 groups according to formulation of initial prescription: film or tablet. Time to treatment discontinuation and monthly health care charges by treatment phase (before treatment, initiation period, during treatment, discontinuation period, after discontinuation, and reinitiation period) were compared between the 2 groups, adjusting on baseline characteristics (demographics, comorbidities, treatment and resource utilization before treatment).

RESULTS: Analysis included 1,847 patients initially treated with film, and 1,318 treated with tablet, followed over 8.0 and 10.9 months on average, respectively. Of those treated with tablet, 13.20% of patients switched to film. Patients treated with film were on average 1.2 years younger at treatment initiation (P = 0.01) and were less likely to be diagnosed with a mental disorder (P = 0.04). The average dose at initiation was higher in the film group. The proportion of patients persistent at 6 months was higher in the film group than in the tablet group (58.46% vs. 63.26%, P = 0.03). The hazard ratio for treatment discontinuation with film versus tablet, adjusted on baseline characteristics, was 0.83 (P = 0.02). Monthly charges were highest around the time of treatment initiation and discontinuation. Monthly charges during treatment were $2,445 for patients treated with film and $3,265 with tablet (P = 0.005). Monthly costs during treatment discontinuation were 42% lower among patients treated with film (P = 0.006).

CONCLUSIONS: Patients treated with BUP/NAL film appear to have a lower probability of early treatment discontinuation. Treatment with the film formulation may generate charge savings, since charges around discontinuation are relatively high, and charges after treatment discontinuation were found to be lower among patients previously treated with film.

SPONSORSHIP: This research was funded by Reckitt Benckiser, Richmond, VA.

■ Rheumatoid Arthritis Specialty Drug Utilizers Cost of Care Trends 2008 to 2010: An Integrated Medical and Pharmacy Claims Analysis

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BACKGROUND: In 2011, autoimmune drugs for rheumatoid arthritis (RA) accounted for 5.5% of all pharmacy benefit (Rx) costs, and the average per prescription cost was $1,590, an increase of 13.5% from 2010, among a 90,000-member commercially insured cohort. It is unknown if the increases in RA drug costs are associated with decreases in medical costs.

OBJECTIVE: To describe the cost of care trends among commercially insured individuals utilizing an RA specialty drug stratified by specialty and nonspecialty costs within the medical and Rx benefits.

METHODS: Integrated Rx and medical claims data from 1.2 million commercially insured members were queried. Members were required to be age 0 to 64 and continuously enrolled for a full year during 2008, 2009, or 2010. RA diagnosis was defined as (a) 2 or more medical claims with an RA ICD-9-CM diagnosis code; (b) 1 medical claim with RA and 1 RA drug claim; or (c) 2 or more RA drug claims. Only drugs that have been FDA approved for RA were used in diagnosis criteria (anakinra, leflunomide, tocilizumab, abatacept, and gold salts). Specialty drugs were defined as anakinra, tocilizumab, abatacept, rituximab and tumor necrosis factor (TNF)-blockers. Annual prevalence of members with an RA diagnosis and drug treatment was identified. For specialty drug utilizers, the annual average per patient total cost of care was calculated. Total cost of care was also separated into 4 categories: medical RA specialty drug, medical all other, Rx RA specialty drug, and Rx all other. Costs were the total paid amount, which includes both the member

| Specialty Drug Utilizers Cost of Care Trends 2008 to 2010: An Integrated Medical and Pharmacy Claims Analysis |

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*Commercially insured members continuously enrolled during analysis year. RA = rheumatoid arthritis.
share and insurer payments. The compound annual growth rate (CAGR) was used to describe cost trends.

RESULTS: RA diagnosis prevalence was 41 per 10,000 continuously enrolled members in 2008 (4,251 of 1,038,638) and increased slightly to 43 per 10,000 in 2010 (4,398 of 979,739). RA specialty drug utilization among members with a diagnosis was consistent over the 3 years at a rate of 1,471 (34.6%) of 4,251 members in 2008 and 1,556 (35.4%) of 4,398 members in 2010. Although RA drug utilization remained constant, the total cost of care CAGR was 7.3% from 2008 to 2010 (figure). All other medical costs were $11,252 in 2008 and increased to $13,710 in 2010, CAGR 10.4%. Combined RA medical and Rx specialty drug costs accounted for 54.7% ($16,218 of $29,652) of the total cost of care in 2008 and was slightly lower at 53.0% in 2010 ($18,098 of $34,163), CAGR 5.6%. The medical and Rx specialty drug CAGRs over the 3-year period were 2.7% and 6.9%, respectively. RA specialty drug costs were approximately 70% from the Rx benefit.

CONCLUSIONS: In 2010, RA medical and Rx specialty drug costs were more than half of the total cost of care. The fastest growing category within the total cost of care was all other medical costs at 3.9 times the rate of all other medical RA specialty drug costs (CAGR 10.4% vs. 2.7%) suggesting that RA specialty drugs are not decreasing medical costs. While specialty drug utilization was relatively flat from 2008 to 2010, the RA category should continue to be monitored because of new drugs coming in the pipeline. Health plans and insurers need to have a full understanding of where dollars are being spent in conditions such as RA and develop management programs to ensure the most effective RA drug therapy use.

SPONSORSHIP: This research was conducted by Prime Therapeutics LLC, Eagan, MN, without external funding.

Specialty Drugs Are Forecasted To Be 50% of All Drug Expenditures in 2018

**Johnson S.** Gunderson B, Bowen KL, Starner CI, Gleason PP. Prime Therapeutics LLC, 1305 Corporate Center Dr., Eagan, MN 55121; sjohnson@primetherapeutics.com, 612.777.5072

BACKGROUND: Specialty drugs include biologics and other drugs that require special handling, are typically injected, and are more expensive than traditional small molecule oral drugs. Billed via either the medical or pharmacy benefit, specialty drugs are historically associated with rare medical conditions such as hemophilia. More recently, however, specialty drugs have come to dominate the treatment of more common chronic conditions such as rheumatoid arthritis and multiple sclerosis. The increase in new specialty drug approvals and progressive price increases have resulted in the need for payers to forecast specialty drugs expenditures separately from nonspecialty traditional drugs.

OBJECTIVE: To integrate medical and pharmacy drug expenditures from 2005 through 2011, trend these expenditures by specialty and traditional drugs, and forecast when specialty drugs will become 50% of all drug expenditures.

METHODS: Prime Therapeutics’ integrated medical and pharmacy database of 9 million currently active commercially insured members was queried to identify monthly drug specialty and nonspecialty expenditures. Specialty drugs were defined as all drugs on the Prime Therapeutic pharmacy benefit specialty drug management list and most medical benefit processed drugs (e.g., J-codes) with the complete exclusion of vaccines and diagnostics. All drug claims not classified as specialty were defined as nonspecialty. From January 2005 to December 2011, the monthly proportion of specialty drug expenditures out of the total drug expenditures was calculated. To obtain the expenditure trend, the specialty and nonspecialty per member per month total paid (PMPM) monthly percentage increase in expenditures using a rolling 12-month method was calculated from January 2007 to December 2011. The forecast was calculated from the combined specialty medical and pharmacy benefit and the nonspecialty 5-year historical trends.

RESULTS: In 2005, specialty drugs represented 16% of all drug (medical and pharmacy benefit) expenditures, but by December 2011, specialty drugs had become 26.8% of all drug expenditures (see figure). From 2007 through 2011, nonspecialty drug PMPM rolling 12-month trend values had remained in the single digits, starting at 1.4% in January 2007 and ending at -2.5% in December 2011. The rolling 12-month nonspecialty drug trend PMPM values were in the middle teens, starting at 13.5% in January 2007 and ending at 15.7% in December 2011. Assuming a specialty PMPM trend of 15% and a nonspecialty trend of zero, specialty drug expenditures were forecasted to be 50% of total drug spend by 2018.

CONCLUSIONS: Health insurers should utilize integrated medical and pharmacy data when performing specialty drug trending and forecasting. The double-digit specialty drug trends coupled with the flat nonspecialty drug trend have resulted in an increased importance of focusing health insurer resources toward managing specialty drugs. Health insurers will need to increase their vigilance of specialty drugs to encourage the most cost-effective use.

SPONSORSHIP: This research was conducted by Prime Therapeutics LLC, Eagan, MN, without external funding.

Store and Prescription Characteristics Associated with Primary Medication Nonadherence

**West-Strum D.** Bentley J, Holmes E, McCaffrey D, Pace P, Porter J, Wasson M. The University of Mississippi, P.O. Box 1848, Facer Hall 225, University, MS 38677; dwest@olemiss.edu, 662.915.1071

BACKGROUND: Primary medication nonadherence (PMN) is any instance whereby patients fail to initiate a pharmacotherapy regimen after receiving a prescription for a new therapy. Currently, there is little in the literature that provides information on how to measure PMN across pharmacies and what factors are related to PMN. The Pharmacy
Quality Alliance (PQA) has developed a quality measure to assess the rates of PMN in pharmacies. The PMN measure is calculated by dividing the number of unclaimed (not picked up after 30 days) electronic prescriptions for newly initiated drug therapy (or appropriate alternative) by the total number of electronic prescriptions for newly initiated drug therapy during the measurement period (for patients 18 years and over). The measure only includes drugs for chronic conditions.

**OBJECTIVE:** To measure PMN in a grocery chain pharmacy and to identify the prescription-level (prescriber and patient) and store characteristics associated with PMN.

**METHODS:** The PQA-developed PMN measure was used, and PMN rates were calculated for 100 pharmacies in a large grocery chain as well as an overall rate. The grocery chain provided de-identified, transactional data for calendar years 2009-January 2012 (de-identified, unique patient and store codes were available). Investigators examined adult individuals with a new electronic prescription for any of a number of medications included in the PQA PMN measure during the measurement period and determined whether the medication (or appropriate alternative) was claimed within 30 days. The wash-out period for the data was 180 days prior to January 1, 2011. This period was used to determine that a prescription was a newly initiated prescription for the patient. The PMN measurement period was from January 1, 2011, to December 31, 2011 (plus 30 days after to assess whether prescriptions were claimed). Prescription-level (patient and prescriber characteristics associated with a prescription) and store-level predictors of whether a prescription was unclaimed were assessed using multilevel logistic regression with a random intercept. PROC GLIMMIX in SAS version 9.3 was used for the analysis.

**RESULTS:** Of the e-prescriptions during the 1-year observation period, 29,238 were for new therapy as defined by the PMN measure, and 3,570 (12.2%) of those new prescriptions (or drug alternatives) were not claimed within the 30-day period. There was significant variability among the 100 pharmacies. The estimated odds of an unclaimed prescription were different significantly among drug classes comprising the PQA PMN measure ($P<0.0001$) and were higher as out-of-pocket costs increased ($P<0.0001$), when the prescription was accompanied by another prescription on the same day ($P<0.0001$) and for primary-care and specialist physicians relative to physician assistants and advanced practice nurses ($P=0.0002$). The estimated odds were slightly higher for younger individuals ($P=0.0008$) and when dispensed at stores with lower prescription volumes ($P=0.0017$). Neither the gender of the patient ($P=0.733$) nor the payment source ($P=0.543$) were related to whether the prescription went unclaimed in the multivariable model.

**CONCLUSIONS:** Based on the calculated rates, PMN is a significant problem in this setting. Efforts directed at further understanding of this behavior and how to reduce its occurrence are warranted.

**SPONSORSHIP:** This research was funded by NACDS Foundation, Alexandria, VA.

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**Suboxone Duration of Therapy for Members with Concurrent Opioid Use**

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**BACKGROUND:** Americans consume 80% of the global opioid supply and 99% of the global hydrocodone supply. Suboxone is covered for opioid dependence after a prior authorization is completed confirming an opioid dependence diagnosis and enrollment in a drug addiction treatment program. If criteria are met, the authorization may be renewed every 6 months. Currently there is no clinical evidence guiding the appropriate Suboxone treatment length. A patient safety program uses retrospective claim review to identify members who have overlapping Suboxone and opioid or tramadol pharmacy claims. Letters are mailed...
to Suboxone prescribers informing them of overlapping pharmacy claims. A week following mailing, a pharmacist contacts Suboxone and opioid prescriber(s) by telephone to ensure awareness of the concomitant use. If a member continues to fill opioids/tramadol, future opioid/tramadol pharmacy claims may be denied.

**OBJECTIVE:** To identify members who are taking Suboxone and filling opioids/tramadol, determine if members will continue Suboxone treatment after opioids are filled, assess need for further intervention to help members achieve Suboxone treatment success, and evaluate the Suboxone prior authorization approval time period.

**METHODS:** Paid Suboxone pharmacy claims were evaluated for those members who were identified as filling Suboxone and opioids/tramadol to determine Suboxone length of therapy duration. Additionally, coverage eligibility was analyzed for at least 6 months following the first Suboxone claim.

**RESULTS:** Descriptive statistics and a scatter plot describing the relationship between length of continuous eligibility and enrollment were produced. The scatter plot strongly suggested a linear relationship between total length of eligibility and length of Suboxone therapy. A regression analysis of the 2 variables captured 82% of the variation ($r^2 = 0.82$). The range of days supplied duration for Suboxone was 1 to 105 months. The linear relationship suggests that members who maintain their insurance coverage continue to fill Suboxone. 60% of members assessed who were eligible for coverage for a year did fill Suboxone for a year. 126 of 880 members (14%) quit filling Suboxone after 1 month even though they were eligible for coverage for 7-18 more months.

**CONCLUSIONS:** Many members fill Suboxone for the duration of coverage eligibility. Most members will continue Suboxone treatment after filling opioids/tramadol. Members assessed either continued receiving Suboxone for the duration of coverage eligibility (60%), stopped filling after less than 3 months of Suboxone treatment (23%), or received at least 3 months of Suboxone but did not continue to fill Suboxone for the duration of coverage eligibility (17%). The 14% of members who quit filling Suboxone after 1 month are possible treatment failures, who may continue abusing opioids. A root-cause analysis may assist in identifying how the patient safety program may be enhanced to better assist these members. Since many members take Suboxone for years, extending the Suboxone prior authorization approval period to 12 months may be more time and cost efficient for both the provider and prior authorization department.

**SPONSORSHIP:** This research was conducted by Aetna Inc., Hartford, CT, without external funding.

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**The 2012 U.S. Payor Landscape: Results from a Survey of Medical and Pharmacy Directors on Comparative-Effectiveness Research**

**Brook RA,* Smeeding J, Mehr SR, Carlisle JA. JeSTARx Group & TPG-NPRT, 18 Hirth Dr., Newfoundland, NJ 07435; RBrook@JeSTARx.com, 973.208.8621**

**BACKGROUND:** To control the growth of health care costs and ensure appropriate utilization of products, payors use a variety of formulary management tools. Current efforts by governments, quasi-governmental entities, and private-public collaborations to introduce better comparative study information to the formulary decision-making process is underway.

**OBJECTIVE:** To determine the types of approaches preferred by medical and pharmacy directors of U.S. health plans, insurers, and pharmacy benefit managers to enhance the pharmacy and therapeutics (P&T) decision-making process and how medications accepted onto the formulary should be covered.

**METHODS:** This study used an online interactive survey of U.S. medical and pharmacy directors (MDs and PDs, respectively). In addition to a 10-point Likert scale (1 = agree completely, 10 = disagree completely), some questions used qualitative responses and interpretive analysis to explore beliefs about certain statements.

**RESULTS:** The respondents represented 44 commercial plans, 19 Medicaid plans (14 HMO/PPO and 5 traditional fee for service [FFS]), and 23 Medicare plans (8 FFS, 15 HMO/PPO). The study participants were asked specifically about their expectations for and use of comparative-effectiveness research (CER) data. Respondents indicated that current progress in obtaining usable CER information was slow, with an average rating of only 4.17 (MD = 4.06; PD = 4.40) on the 10-point scale. However, they anticipated regularly utilizing CER information in formulary decision making by 2015 (average rating = 6.03 [MD = 6.0; PD = 6.1]). Their rating of the use of evidence-based medicine in coverage decision making today was somewhat higher, at an average of 7.08 (MD = 7.38; PD = 6.40). The survey participants pointed out that emerging CER results will greatly affect the following areas: optimization/improvement of clinical guidelines (22.6%), medical/pharmacy benefit management (19.4%), evaluation of the value (16.1%), appropriateness of care (36.1%), pharmaceutical research and development (6.5%), with 16.1% unsure or uncertain. When asked about how they would change their plans’ or PBMs’ pharmacy benefit design, the most frequent responses were incorporating CER data into copayment tiering and management (33.3%), further incentivizing adherence through benefit design (10.0%), and altering benefit design structures for specialty pharmaceuticals (10.0%; primarily to lower member out-of-pocket costs). In regard to improving their plans’ PBMs’ P&T committee process, 23.3% offered that they would use more CER results in the decision-making process, 13.3% would enhance the physician/specialist presence on the review committee, and 6.6% mentioned that they would increase the time allowed for review to allow for a more in-depth evaluation.

**CONCLUSIONS:** The environment for P&T committee decision making in managed care is undergoing a series of changes, and payer medical directors and pharmacy directors, who commonly serve as P&T committee members, have distinct opinions as to how to alter the process to adapt to these influences.

**SPONSORSHIP:** This research was conducted by TPG National Payor Roundtable, Glastonbury, CT, and JeSTARx Group, Newfoundland, NJ, without external funding.

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**The Effect of Medication Therapy Management (MTM) Services on the Costs of Diabetes Patients with Complications: A Retrospective Medical Claims Analysis**

**Soliman AM,* Carlson AM, Dowd B, Brummel A. University of Minnesota College of Pharmacy, 308 Harvard St., SE, Minneapolis, MN 55455; soliman008@umn.edu, 612.333.7804**

**BACKGROUND:** Various studies have examined the association between medication therapy management (MTM) services and management of chronic diseases. However, few reports track the sustained impact of MTM on medical costs over time.

**OBJECTIVE:** To estimate the financial impact of exposure to MTM services on medical costs for patients with complex diabetes compared with a less complex control group with diabetes who did not receive MTM services during an 18-month demonstration period.

**METHODS:** This retrospective cohort study examined medical claims of state employees with a diagnosis of diabetes and exposed to MTM services (n = 101) at Fairview Health Systems clinics during a pilot program that started in August 2007. Data for the 6 months prior to the first MTM visit (index date for the MTM group) and 18 months following
were analyzed. Results were compared with state employees who had diabetes but were not exposed to MTM (n=80, index date defined as first medical claim that occurring after August 1, 2007). Multivariate generalized linear regression models with gamma distribution and log link functions were used to estimate the potential differences in total medical costs between the 2 study groups controlling for age, sex, a modified Charlson score, complexity of diabetes, and occurrence of hospitalization in the baseline period for each 6-month period (baseline and 3 subsequent 6-month periods). A multivariate repeated measures generalized linear regression model with gamma distribution and log link function within a generalized estimating equations framework (GEE) was used to estimate the potential differences in medical costs between the 2 study groups in 18 months following the index date. Patients' claims in the baseline period (6 months pre-index) were used to define the diabetes complexity variable (presence of diabetes complications such as cardiovascular diseases, hypertension, renal disease, and hyperlipidemia identified through ICD-9-CM codes). The modified Charlson index included only those conditions not already controlled for in defining the complexity of diabetes. Hospitalizations were determined using room and board specific revenue codes and/or CPT codes specific for inpatient services.

RESULTS: T-tests and chi-square analysis found no significant differences between the study groups at the 0.05 level with the exception of diabetes associated complications, which was significantly higher in the MTM group (72.3% vs. 18.8%; P<0.001), suggesting a more complex diabetes presentation in the MTM group. While the MTM group had significantly higher adjusted medical costs for the 6 months prior to index date ($14,261 vs. $8,727; P=0.01), nonsignificant differences were found at each of 3 consecutive 6-month post-MTM period comparisons: months 1-6 ($11,778 vs. $9,510); months 7-12 ($14,608 vs. $15,155); and months 13-18 ($9,242 vs. $8,806). The GEE repeated measures model showed that marginal adjusted costs were not significantly different between the 2 groups over the entire 18-month period ($14,793 vs. $11,483; P=0.43).

CONCLUSIONS: Exposure to MTM services resulted in overall reduction in medical costs for more complex patients with diabetes, moving them towards an economic burden equivalent to that of less complex diabetes patients. MTM services contribute to cost management strategies of value to health plans and self-insured employers.

SPONSORSHIP: This research was conducted by the University of Minnesota Graduate School, Minneapolis, MN, without external funding.

Time to Discontinuation of Newly Initiated Biologic Therapy for Adult Crohn’s Disease (Infliximab Versus Adalimumab) and for Rheumatoid Arthritis (Infliximab Versus Adalimumab or Etanercept)

Bowen KL,* Gleason PP. Prime Therapeutics LLC, 1305 Corporate Center Dr., Eagan, MN 55121; kbowen@primetherapeutics.com, 612.777.5436

BACKGROUND: The 3 most commonly used tumor necrosis factor (TNF) blockers are the self-injectables adalimumab and etanercept, which are generally billed via pharmacy benefit, and intravenously infused infliximab, which is generally billed via medical benefit. All 3 are FDA approved to treat rheumatoid arthritis (RA), and infliximab and adalimumab are both approved for adult Crohn’s disease. Adult Crohn’s and RA treatment represent more than half of TNF blocker use. As insurers develop TNF blocker management strategies, it is important to understand the comparative effectiveness of these agents within their managed populations.

OBJECTIVE: To compare the time to discontinuation (d/c) of newly initiated biologic treatment of adult Crohn’s disease using infliximab or adalimumab and of newly initiated biologic treatment of RA using infliximab, adalimumab, or etanercept. Earlier d/c may indicate a less effective therapy.

METHODS: Integrated pharmacy and medical claims data from commercially insured members younger than 65 years were used to identify members with a first claim in either 2010 or 2011 for infliximab, adalimumab, or etanercept, which was preceded by at least 365 days of continuous enrollment but no prior biologic claim, defined as abatacept, adalimumab, anakinra, certolizumab pegol, etanercept, golimumab, infliximab, tocilizumab, or rituximab. Using ICD-9-CM diagnosis codes on all medical claims, members were assigned their most frequently coded diagnoses among the FDA-approved indications and limited to those assigned RA or Crohn’s disease (and older than 18 years). Kaplan-Meier analysis was used to calculate and present the time to d/c of therapy, defined as the first adalimumab or etanercept claim followed by a gap of more than 60 days plus the days supply, the first infliximab claim followed by a gap of more than 120 days, or a switch to a different biologic agent. Members were followed to d/c, disenrollment from plan, or December 31, 2011 (up to 24 months), with censoring at the time of disenrollment or December 31, 2011. A log rank test was used to statistically compare time with d/c stratified by drug for Crohn’s and for RA.

RESULTS: There were 1,003 members who met study criteria for adult Crohn’s: 494 infliximab and 509 adalimumab, respectively, 48.9% and 52.3% female, with mean age 38.5 and 39.5. Duration of therapy was significantly shorter for the Crohn’s infliximab patients (log rank chi-square 6.07, P=0.0138), with 25% d/c by 4 months and 50% by 16 months compared with 6 and 22 months, respectively, for adalimumab. There were 2,821 members who met criteria for RA: 284 infliximab, 1,301 adalimumab, and 1,236 etanercept, respectively, 72.5%, 77.2%, and 74.4% female, with mean age 50.0, 48.1, and 47.8. Duration of therapy was not significantly different among the RA infliximab, adalimumab, and etanercept patients, with 25% d/c for each agent by less than 4 months and 50% of each by about 13 months.

CONCLUSIONS: Time to d/c was not found to be different among members with RA started on these 3 agents. Adalimumab new starts for Crohn’s treatment persisted on therapy significantly longer than
infliximab. These findings are observational and may reflect differences between patients selected to receive 1 therapy over the other. Further research should be performed to assess other outcomes, such as disease control and costs.

**SPONSORSHIP:** This research was conducted by Prime Therapeutics LLC, Eagan, MN, without external funding.

### Treatment Patterns and Health Care Cost of Oncology Patients Treated with Bevacizumab in Hospital Outpatient and Office Settings

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**BACKGROUND:** Declining health plan reimbursements for physician-administered chemotherapy have led to speculation and initial evidence that the population of oncology patients may be shifting from physician offices (OFF) to hospital outpatient clinics (HOS). The extent to which this applies to oncology patients treated with bevacizumab and whether the effect varies by tumor type is unclear.

**OBJECTIVE:** To examine treatment patterns and costs for patients in each site of service.

**METHODS:** This retrospective study used medical and pharmacy claims (2006-2011) from a national U.S. health plan to identify oncology patients (aged 18 years or older) initiating treatment with bevacizumab; diagnoses included metastatic colorectal cancer (CRC), lung cancer (LC), and other cancers. Patients were required to be enrolled in the health plan for 6-months pre- and 6-months post-initiating bevacizumab, patients who died were retained in the study. Patients were stratified into cohorts based upon the location of bevacizumab treatment: HOS or OFF. A 6-month baseline period assessed patient characteristics; a variable follow-up period (until discontinuation of bevacizumab, disenrollment, or March 2011) assessed treatment patterns, utilization, and costs. Weight-based dose per administration was estimated based on population average weights.

**RESULTS:** A total of 3,216 qualifying oncology patients initiated bevacizumab treatment, with 219 HOS and 2,997 OFF patients. A significantly higher proportion of HOS patients were in Medicare Advantage plans (78.08% for HOS vs. 17.82% for OFF; P < 0.001), and HOS patients were older on average (mean age 66.63 years in HOS vs. 59.20 years in OFF; P < 0.001). Among CRC patients (n = 1,171) and LC patients (n = 911), 6.40% and 6.59%, respectively, initiated bevacizumab in the HOS setting. The proportion of patients receiving bevacizumab in HOS settings increased over time, and differences between OFF and HOS in dose administered narrowed over time (table). Duration of therapy was shorter in HOS (210 days in OFF vs. 182 days in HOS; P = 0.003), and a Cox proportional hazards model found HOS patients were more likely to discontinue therapy after adjusting for patient characteristics (HR of discontinuing therapy in HOS vs. OFF: 1.19, 95% CI: 1.03, 1.38). Multivariate analysis indicated that costs were, on average, 9.6% higher for the HOS cohort (P < 0.001) after adjusting for patient characteristics, with variation by tumor type. Cost per infusion were higher in HOS ($9,513) than in OFF ($6,672), P < 0.001.

**CONCLUSIONS:** This study found that the percentage of patients treated in the HOS setting increased over time. HOS patients were associated with higher average costs and shorter treatment duration compared with OFF. Bevacizumab’s label indicates that patients should be treated until disease progression. The implications of the shorter duration of treatment in the HOS setting are unclear, since claims data cannot provide reasons for treatment discontinuation. Further investigation of the shift to hospital outpatient treatment is warranted.

**SPONSORSHIP:** This research was funded by Genentech, Inc., South San Francisco, CA.

### Treatment Patterns in Patients with HER2+ or ER/PR+ Metastatic Breast Cancer

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**BACKGROUND:** The determination of hormone and HER2 status is an important pathological component to predicting the outcomes and prognoses of patients with metastatic breast cancer (mBC). While treatments for HER2+ and ER/PR+ have improved over the past decade, little research has been conducted on whether these treatments are reflected in real-world treatment patterns. This is in part large because most secondary data sources do not track hormone status.

**OBJECTIVE:** To examine treatment patterns across multiple cohorts of HER2+ and ER/PR+ mBC patients.

**METHODS:** The Varian Medical Oncology electronic medical record (EMR) database of outpatient oncology clinic data from the United States was used to identify 3,994 women with a diagnosis of mBC between January 1, 2003, and December 31, 2010, of which hormone status was available on 2,404 women. The HER2+ and ER/PR+ patients were each divided into 2-year cohorts based on index diagnosis date of metastatic disease to examine relative use of treatment regimens over time and line of therapy.

**RESULTS:** Of 2,404 women, 223 were HER2+ and 789 were ER/PR+. Baseline characteristics were similar for both groups in terms of age, race, duration of disease, and stage at diagnosis. Across all HER2+ cohorts, first-line (1L) use of trastuzumab (T), either alone or in combination, ranged from 50%-57%. T-taxane-platin regimens were most common. Prior to 2007, cyclophosphamide/doxorubicin regimens were used in 11%-15% of patients. In third-line (3L) use, T was part of 61%-71% of the regimens, with capcitabine/T, anastrozole/T, and vinorelbine/T combinations being the most frequent. Across all ER/PR+ 1L cohorts, single-agent anastrozole (9%-13%) and letrozole (9%-17%) were used most frequently, followed by fulvestrant and capcitabine. Cyclophosphamide/doxorubicin use decreased from 16.5% in 2006 to 1.4% in 2010. Among the 2L patients, paclitaxel use was highest in 2006.

**TABLE**

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<td></td>
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<td>4.41</td>
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<tr>
<td></td>
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<td>2010</td>
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<td></td>
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<td>88.97</td>
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<td></td>
<td>11.03</td>
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<td>4.51</td>
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<td>4.12</td>
</tr>
</tbody>
</table>

<sup>a</sup>P < 0.001.

HOS = hospital outpatient clinics; mg/kg = milligrams to kilograms; OFF = physician offices.
OBJECTIVE: To examine the trend in benzodiazepine utilization under Medicare Part D in U.S. outpatient settings.

METHODS: This project proposed a secondary data analysis using a national longitudinal database. Data was extracted from the National Ambulatory Medical Care Survey (NAMCS) between January 2005 and December 2009. Subjects were derived from ambulatory physician office visits where the primary payment source was Medicare, and at least 1 FDA-approved benzodiazepine was prescribed. A series of descriptive statistics were used to estimate the national weighted frequency of each FDA-approved benzodiazepine was prescribed. A series of descriptive statistics were used to estimate the national weighted frequency of each benzodiazepine used in U.S. outpatient settings.

RESULTS: There were an estimated 4.85 billion visits to office-based physicians in the United States from 2005 to 2009 of which 1.18 billion (24.26%) were made by Medicare recipients. 86.52 million (7.3%) of these Medicare visits received at least 1 FDA-approved benzodiazepine prescription, including Alprazolam (33.4%), Lorazepam (21.2%), Clonazepam (16.3%), Diazepam (12.2%), Temazepam (7.5%), Midazolam (6.1%), Clorazapate Potassium (1.6%), Triazolam (0.8%), Oxazepam (0.8%), Flurazepam Hydrochloride (0.7%), Chlordiazepoxide Hydrochloride (0.4%), Estazolam (0.17%), and Quazepam (0.02%). After 1 year of Medicare Part D, benzodiazepine use for Medicare patients decreased 1.38% from 14.72 million in 2005 to 14.52 million in 2006. However, the usage dramatically increased 20% from 14.52 million in 2006 to 17.43 million in 2007 and continuously raised to 21.72 million in 2009. Weighted regression analysis showed a significant linear trend for benzodiazepine use during the 5-year study period (P = 0.014, adjusted R² = 0.8625).

CONCLUSIONS: The study findings indicated that benzodiazepine use was not affected by the Medicare Part D formulary exclusion program. Interestingly, its usage has been continuously increasing since 2007. Several factors could explain this phenomena: (a) low costs of these drugs and patients willing to pay out of pocket; (b) physicians prescribing privilege; (c) Medicare supplement program; and (d) NAMCS data limitations. Although benzodiazepines will be allowed on Medicare Part D formularies in 2013, there is an extraordinary responsibility on the part of policy makers to respect individualized clinical decisions and suggest appropriate evidence-based intervention.

SPONSORSHIP: This research was funded by sanofi, Cambridge, MA.

Trend in Benzodiazepine Utilization Under Medicare Part D in U.S. Outpatient Settings, 2005 to 2009

Lai LL, Elusma C, Huh G, Koodie N, Ting A. Nova Southeastern University, Fort Lauderdale, FL, without external funding.

BACKGROUND: Since 2006, Medicare Part D has excluded benzodiazepine prescriptions from coverage due to its significant side effects in the elderly. However, this formulary exclusion has raised serious concerns over the potential consequences for poor health outcomes and resulting higher overall health care costs.

OBJECTIVE: To verify whether the treatments reflect general practice and adherence to National Comprehensive Cancer Network guidelines.

METHODS: This research was conducted by Nova Southeastern University, Fort Lauderdale, FL, without external funding.

CONCLUSIONS: This retrospective cohort study highlights the changes that have occurred over the past decade in the treatment of patients with HER2+ and/or PR+ mBC in the United States. A decline in the use of anthracyclines as 1L therapy was observed, similar to a recent publication on adjuvant treatment in a Medicare population, although in contrast, no corresponding increase in taxane use was noted. Due to incomplete data on the HER2 and hormonal status of mBC patients, and small sample sizes in 3L-treated patients, additional research is needed to verify whether the treatments reflect general practice and adherence to National Comprehensive Cancer Network guidelines.

SPONSORSHIP: This research was funded by sanofi, Cambridge, MA.

OBJECTIVE: To examine the trend in benzodiazepine utilization under Medicare Part D in U.S. outpatient settings.

METHODS: This project proposed a secondary data analysis using a national longitudinal database. Data was extracted from the National Ambulatory Medical Care Survey (NAMCS) between January 2005 and December 2009. Subjects were derived from ambulatory physician office visits where the primary payment source was Medicare, and at least 1 FDA-approved benzodiazepine was prescribed. A series of descriptive statistics were used to estimate the national weighted frequency of each benzodiazepine used in U.S. outpatient settings.

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CONCLUSIONS: The study findings indicated that benzodiazepine use was not affected by the Medicare Part D formulary exclusion program. Interestingly, its usage has been continuously increasing since 2007. Several factors could explain this phenomena: (a) low costs of these drugs and patients willing to pay out of pocket; (b) physicians prescribing privilege; (c) Medicare supplement program; and (d) NAMCS data limitations. Although benzodiazepines will be allowed on Medicare Part D formularies in 2013, there is an extraordinary responsibility on the part of policy makers to respect individualized clinical decisions and suggest appropriate evidence-based intervention.

SPONSORSHIP: This research was conducted by Nova Southeastern University, Fort Lauderdale, FL, without external funding.

Trend in Utilization and Cost of Conventional and Biologic Therapies for Rheumatoid Arthritis

Mostovoy L*, Szychowski J, Brown F, Matlin O, Akinbosoye O. CVS Caremark, 1900 Hamilton St., Philadelphia, PA 19130; lisa.mostovoy@caremark.com, 267.687.2460

BACKGROUND: Rheumatoid arthritis (RA) is an autoimmune disorder that poses a significant public health burden. The treatment of RA has evolved dramatically over the past few decades with the availability of conventional disease-modifying antirheumatic drugs (DMARDS) as well as newer biologic DMARDS for more severe disease. The American College of Rheumatology (ACR) did not provide guidelines regarding the utilization of biologic agents until 2008, when they recommended the use of conventional DMARDs and/or biologic DMARDs, depending on the stage/progression of the disease, efficacy of current treatment, and presence of other comorbid conditions, among other factors.

OBJECTIVE: To quantify the impact of evolving RA treatment guidelines on cost and utilization trends over a 6-year period in terms of conventional and biologic therapies.

METHODS: This was a retrospective longitudinal study of CVS Caremark de-identified administrative claims data of therapy utilizers between January 1, 2006, and December 31, 2011. The analyses were limited to utilizers of the conventional and biologic therapies used to treat RA and related conditions. Conventional DMARD therapies included auranofin, azathioprine, gold sodium thiomalate, hydroxychloroquine, leflunomide, and methotrexate. Biologic DMARD therapies consisted of anti-tumor necrosis factors (TNFs; adalimumab, anakinra, certolizumab, etanercept, golimumab, and infliximab) and non-TNFs (abatacept, rituximab, and tocilizumab). Utilization and costs were measured on a per-member per-year (PMPY) and per-utilizer per-year (PUPY) basis.

RESULTS: On average, 380,472 pharmacy benefit eligible members used these medications each year. Over the study period, conventional DMARDs accounted for 67% of overall utilization based on days’ supply. The relative utilization of conventional DMARD therapy has steadily declined compared with biologics. In 2006, DMARDs accounted for 77.6% of total days supply; in 2011, DMARDs made up just 56.4%, representing a 27% decline in the relative utilization of these therapies. The relative utilization of biologic therapies nearly doubled over the same time period. Over the 6-year study period, PMPY gross cost of conventional DMARDs decreased 36%, from $0.61 to $0.39. Although there was a decrease in PMPY gross cost experienced between 2007 and 2008, the PMPY gross cost of biologics increased nearly 24%, from $10.91 to $13.48. At the same time, PUPY costs of both types of therapy have grown by 9% in biologics and over 41% in conventional DMARDs.

CONCLUSIONS: Our results show that changes in PMPY costs of these therapies are not fully explained by changes in per-utilizer costs. We observed a significant shift to biologics, as a percentage of overall utilization, as well as an increase in the overall PMPY costs of 24%, while per-utilizer costs grew only 9%. These findings suggest that an increasing number of patients are utilizing biologics in 2011 as compared with 2006. Increased use of biologics in the treatment of RA is in line with
the 2008 ACR clinical treatment guidelines. Based on the most recent 2012 ACR recommendations, as well as emerging treatment options for AR, the trend of increasing biologic use is expected to continue. Study findings support the idea that as therapies evolve, practice guidelines are refined and real-world practice follows.

**SPONSORSHIP:** This research was conducted by CVS Caremark, Northbrook, IL, without external funding.

## Units and Costs of Comparable Insulin Supplied to Patients: Is There a Difference by Manufacturer?

**Eby EL,** *Szymialis RA, Ivanova JI, Desai U, Birnbaum H, Cummings AK, Deschamps KD. Eli Lilly and Company, Lilly Corporate Center, DC 4224, Indianapolis, IN 46285; Eby_elizabeth_l@lilly.com, 248.802.9242*

**BACKGROUND:** Because the active ingredients in insulin products by Eli Lilly (LLY) and Novo Nordisk (NN) have similar pharmacokinetic/pharmacodynamic (PK/PD) profiles, patients with similar characteristics are hypothesized to require similar amounts of comparable insulin regardless of the manufacturer.

**OBJECTIVE:** To compare units per claim per day (units) and costs per claim per day (costs) of comparable LLY and NN insulin products supplied in 2011, adjusting for baseline patient characteristics.

**METHODS:** Patients with ≥1 claim for LLY or NN insulin in 2011 and continuous coverage for ≥6 months before their first insulin claim in 2011 (baseline) were identified from a privately insured claims database (N=16,000,000). Units were calculated by multiplying total quantity per claim (in mL) by strength (1 mL = 100 units) and dividing by total days supplied. Costs were calculated by dividing the cost of a claim to insurers by total days supplied. Costs were estimated separately for patients aged <65 and ≥65 years because costs to insurers for patients aged ≥65 may equal to zero due to Medicare coverage. Generalized estimating equation models, adjusting for baseline differences in patient demographics, comorbidities, endocrinologist visits, insulin pump use, and diabetic medication use, and health plan type, were used to estimate the units and costs for comparable products.

**RESULTS:** 24,616 and 20,705 patients, respectively, had claims for comparable LLY and NN insulins in 2011. At baseline, the cohorts had similar age (58.8 years) and gender distribution (53.1% males) but significantly different profiles for comorbidities, endocrinologist visits, health plan type, and insulin pump and diabetic medication use. After adjusting for baseline differences, the units for all comparable LLY and NN insulins were similar, with the exception of lower units for Humulin N and Humulin R vials (table). The regression-adjusted overall cost was significantly lower for comparable LLY versus NN insulin ($7.19 vs. $7.81; P<0.001 among patients aged <65, and $5.78 vs. $6.93; P<0.001 among those aged ≥65) because greater shares of LLY insulin claims were for vials (70.1% vs. 55.2%) and human insulin (32.0% vs. 15.8%), which had lower costs than pens and insulin analogs, respectively.

**CONCLUSIONS:** In this analysis, patients with baseline-adjusted similar characteristics used similar amounts of comparable insulin regardless of manufacturer. The 2011 overall cost was significantly lower for comparable LLY versus NN insulin because of different product mix.

**SPONSORSHIP:** This research was conducted by Eli Lilly and Company, Indianapolis, IN, without external funding.

### TABLE Regression-Adjusted Units Per Claim Per Day for LLY and NN Insulin Claims in 2011

<table>
<thead>
<tr>
<th>All Comparable Insulin Claims</th>
<th>Number of Claims</th>
<th>Units</th>
<th>LLY Mean ± SD</th>
<th>NN Mean ± SD</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>LLY NN</td>
<td>LLY Mean ± SD</td>
<td>NN Mean ± SD</td>
<td></td>
</tr>
<tr>
<td>By package type</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pens</td>
<td>24,236</td>
<td>27,620</td>
<td>60.6 ± 6.5</td>
<td>66.9 ± 6.5</td>
<td>0.021</td>
</tr>
<tr>
<td>Vials</td>
<td>57,106</td>
<td>34,037</td>
<td>75.4 ± 7.5</td>
<td>78.5 ± 7.5</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>By comparable product</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin lispro pen/insulin aspart pen</td>
<td>17,889</td>
<td>20,520</td>
<td>62.3 ± 6.4</td>
<td>62.6 ± 6.4</td>
<td>0.756</td>
</tr>
<tr>
<td>Insulin lispro vial/insulin aspart vial</td>
<td>29,146</td>
<td>20,775</td>
<td>77.2 ± 9.5</td>
<td>77.5 ± 9.5</td>
<td>0.769</td>
</tr>
<tr>
<td>Insulin lispro mix 75/25 pen/biphasic insulin aspart 70/30 pen</td>
<td>4,880</td>
<td>7,098</td>
<td>80.7 ± 11.2</td>
<td>81.1 ± 11.2</td>
<td>0.889</td>
</tr>
<tr>
<td>Insulin lispro mix 75/25 vial/biphasic insulin aspart 70/30 vial</td>
<td>3,443</td>
<td>3,507</td>
<td>87.9 ± 11.2</td>
<td>87.2 ± 11.2</td>
<td>0.779</td>
</tr>
<tr>
<td>LLY human insulin isophane vial/NN human insulin isophane vial</td>
<td>11,076</td>
<td>2,896</td>
<td>66.3 ± 6.0</td>
<td>71.5 ± 6.0</td>
<td>0.026*</td>
</tr>
<tr>
<td>LLY regular human insulin vial/NN regular human insulin vial</td>
<td>5,933</td>
<td>3,666</td>
<td>60.1 ± 9.4</td>
<td>74.9 ± 9.4</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>LLY human insulin 70/30 vial/NN human insulin 70/30 vial</td>
<td>7,508</td>
<td>3,193</td>
<td>81.5 ± 11.9</td>
<td>85.1 ± 11.9</td>
<td>0.463</td>
</tr>
</tbody>
</table>

*Indicates significance, defined as P < 0.50.

LLY = Eli Lilly, NN = Novo Nordisk, SD = standard deviation.

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**Use of Telaprevir Combination Treatment in Patients with Genotype 1 Chronic Hepatitis C Infection: Treatment Persistence and Early Virologic Response in a U.S. Community Setting**

**Vera-Llonch M,** *Castiglione B, Izano M, Kieffer TL, Oster G. Vertex Pharmaceuticals Incorporated, 130 Waverly St., Cambridge, MA 02139; monserrat_vera-llonch@vrtx.com, 617.961.0527*

**BACKGROUND:** Telaprevir (T) in combination with peginterferon/ribavirin (PR) for 12 weeks, followed by an additional 12 or 36 weeks of PR, is approved to treat chronic genotype 1 hepatitis virus (HCV) infection in adults with compensated liver disease.

**OBJECTIVE:** To examine treatment persistence and early on-treatment virologic response in patients receiving T/PR in a community setting in the United States.

**METHODS:** Using data from a specialty pharmacy in the Mid-Atlantic region, we identified all patients who began T/PR between June 1, 2011, and May 31, 2012, and compiled available data until completion or discontinuation of treatment, data cutoff (August 21, 2012), loss to follow-up, or death, whichever occurred first. Measures of interest included discontinuation of T/PR (and reasons thereof) and on-treatment early virologic response (HCV RNA level) at weeks 4 and 12 among patients on therapy. Time to end of treatment was examined using Kaplan-Meier methods. Virologic response was examined across all patients with available data.

**RESULTS:** Study sample consisted of 1,175 patients; mean (SD) age was 52 (10) years; 61% were male; 29% were black; and 52% were treatment-naïve. Fibrosis status was unknown. Insurance was 58% private, 6% Medicare, 7% Medicaid fee for service, and 29% managed Medicaid. As of data cutoff, information was available for 974 patients: 224 (23%) had completed T/PR, 238 (24%) discontinued T/PR up to week 12; treatment...
Undetectable at Week 12 among patients with available lab data.

RVR = rapid virologic response; eRVR = extended rapid virologic response; EVR = early virologic response; HCV = chronic genotype 1 hepatitis C virus; IU/mL = international units per milliliter; RVR = rapid virologic response.

Prior Treatment for HCV

<table>
<thead>
<tr>
<th>Viral Load, by Week</th>
<th>Treatment Naive</th>
<th>All Patients</th>
<th>Relapsers Only</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=279</td>
<td>N=264</td>
<td>N=86</td>
<td></td>
</tr>
<tr>
<td>&lt;4 IU/mL (RVR)</td>
<td>217 (77.8%)</td>
<td>169 (64.0%)</td>
<td>55 (64.0%)</td>
</tr>
<tr>
<td>Undetectable (RVR)</td>
<td>195 (69.9%)</td>
<td>148 (56.1%)</td>
<td>50 (58.1%)</td>
</tr>
<tr>
<td>43-1,000 IU/mL</td>
<td>54 (19.4%)</td>
<td>71 (26.9%)</td>
<td>27 (31.4%)</td>
</tr>
<tr>
<td>&gt;1,000 IU/mL</td>
<td>8 (2.9%)</td>
<td>24 (9.1%)</td>
<td>4 (4.7%)</td>
</tr>
<tr>
<td>Week 12</td>
<td>N=139</td>
<td>N=134</td>
<td>N=40</td>
</tr>
<tr>
<td>&lt;4 IU/mL (RVR)</td>
<td>126 (90.6%)</td>
<td>121 (90.3%)</td>
<td>39 (97.5%)</td>
</tr>
<tr>
<td>Undetectable (EVR)</td>
<td>125 (89.9%)</td>
<td>117 (87.3%)</td>
<td>39 (97.5%)</td>
</tr>
<tr>
<td>43-1,000 IU/mL</td>
<td>11 (7.9%)</td>
<td>10 (7.5%)</td>
<td>1 (2.5%)</td>
</tr>
<tr>
<td>&gt;1,000 IU/mL</td>
<td>2 (1.4%)</td>
<td>3 (2.2%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Undetectable at Week 4 and Week 12 (eRVR)</td>
<td>93 (66.9%)</td>
<td>79 (59.0%)</td>
<td>29 (72.5%)</td>
</tr>
</tbody>
</table>

*Among patients with available lab data.

was ongoing for 390 patients (40%); and 4 (<1%) of patients had died. During the first 12 weeks, discontinuation rates were 69 (7%) due to futility, 144 (15%) due to side effects (primarily anemia and rash), and 25 (3%) due to noncompliance. HCV RNA levels at week 4 and week 12 are reported in the table.

**CONCLUSIONS:** In patients with genotype 1 chronic HCV infection receiving T/PR—many of whom were black and all with unknown fibrosis status—the incidence of treatment discontinuation by week 12 was 24%. Extended virologic response among those with available HCV RNA at week 12 was 67% in treatment-naive patients and 59% in all treatment-experienced patients.

**SPONSORSHIP:** This research was conducted by Vertex Pharmaceuticals Incorporated, Cambridge, MA, without external funding.

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**Using a Validated Claims Data-Based Algorithm to Evaluate the Effectiveness of Self-Injected Versus Infused Biologics for Rheumatoid Arthritis Claims Data**

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**BACKGROUND:** Administrative claims data contain large amounts of medication, diagnosis, and procedure data obtained for reimbursement purposes. These data have been used to assess safety questions, medication dosing, treatment patterns, and costs, but the absence of clinical outcome measures has limited their use in comparative effectiveness research in rheumatoid arthritis (RA). The large number of biologic agents approved for first-line use in moderate-to-severe RA and their costs make them a key area of interest for formulary decision makers. A recently published algorithm to evaluate effectiveness of biologics for RA was developed and validated against clinical outcomes like the Disease Activity Score in 28 Joints (DAS28) using administrative data from the Veterans Health Administration (VHA) linked to the VA RA registry (VARA). This validated algorithm provides a new opportunity to compare effectiveness of biologics in RA using other administrative data sources.

**OBJECTIVE:** To compare the effectiveness of self-injected subcutaneous (SC) biologics (adalimumab, etanercept, and golimumab) versus intravenously infused biologics (abatacept and infliximab) approved for first-line treatment of moderate-to-severe RA in patients enrolled in commercial health plans.

**METHODS:** Data was obtained from the IMS Lifelink Database, which comprises fully adjudicated medical and pharmaceutical claims for > 70 million unique patients from 80 health plans across the United States. Biologic naïve (no claims for biologics in 6 months pre-index) adult patients with RA initiating treatment between 2007 and 2010, continuously enrolled in the same plan for ≥6 months before and 12 months after their first claim for a biologic were included. First-line biologics with <80 patients and patients with diagnoses of plaque psoriasis, psoriatic arthritis, ankylosing spondylitis, juvenile idiopathic arthritis, non-Hodgkin’s lymphoma, chronic lymphocytic leukemia, Crohn’s disease, or ulcerative colitis were excluded. The claim-based algorithm uses the following criteria to determine lack of effectiveness: low adherence to medication (medication possession ratio [MPR] <80%) or receiving <expected number of infusions), increase in biologic dose or frequency, switching biologics, adding new nonbiologic disease-modifying antirheumatic drugs (e.g., leflunomide), new use of glucocorticoids or an increase in glucocorticoid dose, and >1 parenteral or intra-articular injection. Multivariate analyses to control for differences at baseline were not conducted.

**RESULTS:** Patients taking infused (n=2,108) versus SC biologics (n=6,405) were older (median age 53.0 vs. 51.0; P<0.001). A similar proportion were female (77.7% versus 76.8%; P=0.368). Infliximab was the most commonly used infused agent (67.5%) versus abatacept (32.5%). SC biologics included etanercept (58.7%), adalimumab (40.0%), and golimumab (1.1%). Infused agents were effective in a smaller proportion of patients than SC agents (22.0% vs. 28.6%; P<0.001). Among infused agents, infliximab was effective in a lower proportion of patients than abatacept (18.8% vs. 28.6%; P<0.001). Among SC products, etanercept, adalimumab, and golimumab were effective in 29.9%, 26.7%, and 32.9%, respectively. P=0.006 etanercept versus adalimumab and P=0.548 etanercept versus golimumab.

**CONCLUSIONS:** SC biologics were rated as effective in a higher proportion of patients than infused biologics using the algorithm; however, there was substantial heterogeneity between infused products.

**SPONSORSHIP:** This research was funded by Immunex Corporation, a wholly owned subsidiary of Amgen Inc., and by Wyeth, which was acquired by Pfizer Inc. in October 2009, Thousand Oaks, CA.

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**Using Natural Language Processing to Identify Gout Flares and Evaluating Factors Associated with Refractory Chronic Gout Patients in a Managed Care Organization**

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**BACKGROUND:** Refractory chronic gout (RCG) patients have frequent flares and are associated with increased health care resource use, economic burden, and have a decrease in quality of life. Unfortunately, gout flares are not adequately captured using ICD-9-CM codes. Natural language processing (NLP) offers the potential to identify patients with acute gout flares using a validated, automated, and multidisciplinary technology to extract valuable information from unstructured “free text” in electronic health chart notes.
OBJECTIVE: To identify patients with RCG using multidisciplinary technology and evaluate factors associated with RCG patients in an integrated health system.

METHODS: Patients aged 18 years and older with diagnosis of gout (ICD-9-CM 274.xx) and on urate-lowering therapy (ULT) from January 1, 2007, to December 31, 2010, were identified within Kaiser Permanente Southern California (KPSC). An algorithm containing an extensive list of key words, text phrases, and other search words associated with gout flares was created in collaboration with an NLP specialist and KPSC rheumatologists. RCG patients were defined as patients with >3 gout flares during 12 months of follow-up. Baseline comparisons were made between RCG and non-RCG patients using descriptive statistics. A multivariate logistic regression model was used to evaluate characteristics such as age, gender, race, comorbid conditions, concomitant medications, adherence, prescriber care, and ULT dose adjustment associated with RCG patients.

RESULTS: Of 16,707 gout patients, electronic chart notes were available for 16,519 patients (99%). The mean age was 62 years, and 80% were male. The common comorbid conditions were hypertension (73%), dyslipidemia (55%), diabetes (25%), and renal disease (25%). Over 70% of patients were seen by a primary care physician (PCP) and were prescribed their initial ULT from a PCP. NLP identified 511 patients with RCG with mean serum urate acid (sUA) level of 9.3 mg/dL versus 8.1 mg/dL in non-RCG patients. Following are factors that were found to be statistically significant between the 2 groups: female patients were 23% less likely to be RCG (OR=0.77, 95% CI 0.59–1.01); patients at sUA goal (<6mg/dL) were 69% less likely to be RCG (OR=0.31, 95% CI 0.17–0.56); patients with renal disease (OR=2.03, 95% CI 1.58–2.59) and obese patients were more likely to be RCG (OR=2.04, 95% CI 1.60–2.60); Patients with RCG were more likely to be taking colchicine (OR=2.00, 95% CI 1.61–2.48) and corticosteroids (OR=1.12, 95% CI 0.90–1.40), and RCG patients were more likely to have an increase in their ULT dose (OR=2.27, 95% CI 1.65–3.14).

CONCLUSIONS: NLP is a new, innovative, validated field of computer science and linguistics that can be used to identify and extract valuable information within EHR “free text” chart notes. We identified RCG patients using NLP and identified factors that may contribute to lack of disease control. These factors included failure to achieve sUA level goals, renal disease, greater need for rescue medications (colchicine, corticosteroids), and poor adherence. NLP proved to be a valuable tool and allowed us to identify and characterize RCG patients within an integrated system.

SPONSORSHIP: This research was funded by Savient Pharmaceuticals, Inc., Bridgewater, NJ.

Utilization of Infliximab in the Treatment of Rheumatoid Arthritis in an Ambulatory Care Network in Northern California

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BACKGROUND: Infliximab is a tumor necrosis factor alpha inhibitor approved by the FDA for treatment of rheumatoid arthritis (RA). Demonstration of the “real-world” weight-based utilization patterns of this agent is limited. An understanding of the current usage patterns of infliximab in the treatment of RA is essential to optimizing the management of patients.

OBJECTIVE: To describe the utilization of infliximab in the treatment of RA in an ambulatory care network in Northern California.

METHODS: Patients with an ICD-9-CM diagnosis of RA (714.xx) were retrospectively identified in the electronic health record (EHR) of Sutter Health’s ambulatory network between January 1, 2007, and June 30, 2011 (index period). Adult RA patients (aged ≥18 years) with ≥1 infliximab infusions were included in this analysis, comprising both prevalent and incident users. Patients receiving another biologic agent within 30 days of an infliximab infusion were excluded. Demographics, characteristics, and infliximab dosing and frequency were collected from the EHR. Weight-based dose was calculated by dividing the prescribed dose by the most recent weight recorded in the EHR. Dose changes were defined as an increase or decrease in ≥1 vials used, and infusion frequency changes were defined as a prescribed increase or decrease by ≥1 weeks as compared with the previous infusion. Descriptive statistics were used to summarize study variables. As an exploratory analysis, data were stratified by payer type.

RESULTS: A total of 125 patients with RA were identified. On average, patients were aged 60 years (range 18–90 years); the majority were female (82%), and 65% were concurrently taking methotrexate. Approximately half of the patients were Medicare beneficiaries (53%), and 44% were commercial beneficiaries; the remaining patients were uninsured or had “other” insurance. Patients received infliximab over a mean of 27.4 months at an average prescribed dose of 347.2 mg (range 100 to 875 mg), corresponding to an average weight-based dose of 4.8 mg/kg (range 2.51–11.67 mg/kg). Weight-based doses increased from 4.5 mg/kg at the beginning of the index period to 5.0 mg/kg at the end of the index period. Among 125 RA patients, a total 2,608 infliximab infusions were administered during the study period. Dose increases and decreases occurred in 1.6% and 0.2% of infusions, respectively. The median infusion frequency was 8 weeks (range 2 to 13 weeks). Frequency increases and decreases occurred in 1.8% and 1.5% of infusions, respectively. Medicare beneficiaries were, on average, older than commercial beneficiaries (68.6 vs. 51.3 years) and were less likely to have received prior biologic therapy (91.1% vs. 36.4%). Infliximab dosing (mean: 5.0 and 4.5 mg/kg, respectively) and infusion frequency (median: 8 weeks, for each) were similar for Medicare and commercial beneficiaries.

CONCLUSIONS: In this California ambulatory care network, RA patients were maintained on infliximab for an average of 2.3 years with a median infusion frequency of every 8 weeks. The mean weight-based dose of infliximab was within the range suggested in the approved product labeling. Changes to infliximab dosage or dosing frequency were rare, and there was little variation in the average weight-based dose administered over the study duration.

Utilization of Infliximab in the Treatment of Inflammatory Bowel Disease in an Ambulatory Care Network in Northern California

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BACKGROUND: Infliximab is a tumor necrosis factor alpha inhibitor approved by the FDA for multiple indications including the treatment of ulcerative colitis (UC) and Crohn’s disease (CD), which together comprise inflammatory bowel disease (IBD). Demonstration of the “real-world” weight-based utilization of infliximab is limited. An understanding of current infliximab utilization patterns in the treatment of patients with UC and CD is essential to optimizing the management of patients.
OBJECTIVE: To describe the weight-based utilization of infliximab in the treatment of UC and CD in a large ambulatory care network in Northern California.

METHODS: Patients with an ICD-9-CM diagnosis of UC (556.xx) or CD (555.xx) were retrospectively identified in the electronic health record (EHR) between January 1, 2007, and June 30, 2011 (index period). Adult UC and CD patients (≥ 18 years of age) with ≥ 1 infliximab infusions were included in this analysis, comprising both prevalent and incident users. Patients with a concomitant biologic agent used within 30 days of an infliximab infusion were excluded. Demographics, characteristics, and infliximab dose and frequency were collected from the EHR. Weight-based dose was calculated by dividing the prescribed dose by the most recent weight recorded in the EHR. Dose changes were defined as an increase or decrease in ≥ 1 vial and infusion frequency changes were defined as a prescribed increase or decrease by ≥ 1 week as compared with the previous infusion. Descriptive statistics were used to summarize study variables for the combined population and for patients with UC and CD.

RESULTS: A total of 143 patients with IBD were identified (54.5% with UC and 45.5% with CD). On average, patients were aged 40 years (range 18 to 81 years), and 52% were female. The majority of patients were commercially insured beneficiaries (92%). Patients received infliximab over a mean of 18.5 months at an average prescribed dose of 452.9 mg (range 200 mg to 1,000 mg), corresponding to a mean weight-based dose of 6.0 mg/kg (range 3.7 to 10.6 mg/kg). Weight-based dose increased from 5.7 mg/kg at the beginning of the index period to 6.4 mg/kg at the end of the index period. A total of 1,681 infliximab infusions were administered among 143 IBD patients during the study period. Dose increases and decreases occurred in 2.2% and 0.3% of infusions, respectively. The median infusion frequency was 8 weeks (range 2 to 12 weeks). Frequency increases and decreases occurred in 2.0% and 0.9% of infusions, respectively. UC and CD patients were similar in terms of baseline demographics and characteristics, as well as average infliximab dosing (mean: 5.9 and 6.1 mg/kg, respectively) and infusion frequency (median: 8 weeks, for each).

CONCLUSIONS: In this large California ambulatory care network, IBD patients were maintained on infliximab for an average of 18 months with a median infusion interval of every 8 weeks. Changes to infliximab dosage or dosing frequency were rare, and there was little variation in the average weight-based dose administered over the study duration.

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