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**FACTORS ASSOCIATED WITH
SUBOPTIMAL SAFETY LABORATORY
MONITORING OF METFORMIN THERAPY**

BY

YU SEON JUNG

**A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF THE
REQUIREMENTS FOR THE DEGREE OF
MASTER OF SCIENCE
IN PHARMACEUTICAL SCIENCES**

UNIVERSITY OF RHODE ISLAND

2014

MASTER OF SCIENCE THESIS

OF

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2014

ABSTRACT

The aim of the study is to determine whether the recommended lab monitoring for metformin is performed appropriately in the ambulatory care setting and if the patient characteristics are associated with monitoring rate. A cross-sectional study was performed using a healthcare claims database. An univariate analysis by frequency and percentage assessed the characteristics of patients in our study. Also, it measured the frequency of lab monitoring: HgbA1C, CBC or B12, SCR, and optimal, defined as receiving all three tests. Bivariate analyses determined the significance of differences between those receiving and not receiving lab testing according to patient characteristics. In a prediction model, multivariate logistic modeling with backward elimination was performed to identify significant patient characteristics predicting lab monitoring, and to obtain adjusted odd ratios. Optimal lab monitoring rate during 18 months rate during the 18 month was 32.88 percent. A predictive model included age category, cardiovascular, renal, respiratory disease, mental health disorder, number of clinic visit, and medication possession rate (MPR). Elderly patients with comorbidities were more likely to receive optimal care; more frequent clinic visits and greater rates of medication adherence were associated with receiving optimal lab monitoring for metformin.

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CHAPTER 1

BACKGROUND

Diabetes Mellitus is a global epidemic which affects 8.3% of the United States' population, or 25.8 million in 2010.¹ In 1980, the number of persons diagnosed with diabetes in America was 5.6 million which increased to 20.9 million in 2012.¹ Globally, the incidence of diabetes is increasing dramatically, caused by more urbanization, obesity, and longer-life expectation for patients with diabetes.² Rising number of these patients with diabetes also leads to growing expenditure of diabetes care which had become a great burden to the American society. From 2002 to 2007, the total cost of diabetes has increased from \$132 billion to \$174 billion.³

High expenditure is associated with various complications from diabetes such as retinopathy, nephropathy, coronary artery disease, peripheral artery disease and cerebrovascular disease. Diabetes is the leading cause of a kidney failure. In 2008, diabetes was accountable for 44% of new cases of a kidney failure.⁴ About 60 to 70% of patients with diabetes have mild to severe forms of nervous system damage and they are twice as likely to have depression than people

without diabetes.^{5, 6} In addition to the complications, this population is often obese and has a high cholesterol level and blood pressure. Therefore, other comorbid, metabolic diseases coexist in patients with diabetes; such comorbidities increase the cost of care and complicate patients' drug regimen. Such complex drug regimen and vulnerability of patients with diabetes are significant problems for their care.

According to the current American Diabetic Association (ADA) guidelines for diabetes, metformin is a preferred first-line treatment for the treatment naïve patients with diabetes type II.⁷ Metformin use is prevalent and its safety and effectiveness has been well demonstrated. Hypoglycemia occurs less frequently with metformin than any other oral antidiabetic medications. The common side effects are diarrhea, flatulence, cobalamine deficiency, and asthenia. Serious side effects include lactic acidosis yet this condition is very rare, at 0.03 cases per 1000 patients years.^{8, 9, 10} Although metformin is a fairly safe drug, laboratory monitoring is recommended to avoid anemia, lactic acidosis, or other complications. Vitamin B12 level is recommended to be monitored every 2-3 years and hematologic parameters should be monitored at the baseline and annually to avoid anemia.^{8,9} Also, renal function test (Serum Creatinine, Scr) before initiation and annually thereafter is recommended to monitor the risk

of lactic acidosis. Since a substantial amount of metformin is excreted through kidney, monitoring Scr level is prudent. Additionally, glycosylated hemoglobin (HbA1C) level testing monitors efficacy of the drug; it is also a safety measure to monitor hypoglycemia or to delay or avoid further complication of diabetes.^{8, 9}

In practice, however, metformin is often used without safety monitoring given its reputation for safety. A retrospective study of metformin use in inpatient setting presented that among 204 hospitalized metformin users, 27% had at least one absolute contraindication to metformin.¹⁰ The most common contraindication was elevated serum creatinine concentration in 32 patients (12%). However, metformin was discontinued in only 8 (25%) of these patients. The disconnection of clinical guideline for metformin use and real practice was found in outpatient setting as well. A cross-sectional analysis, conducted in 10 different HMOs, reported that the absence of Scr lab testing at the initiation of metformin therapy was 25.8% (95% CI 15.2-35.9).¹¹ Also, another cross-sectional study with chronic metformin users reported the rate of missing annual Scr testing by 29%, 26%, 25% in 1999, 2000, 2001, respectively.¹² Cell blood count testing was missing more frequently, 80%, 79%, 78% in 1999, 2000, 2001, respectively.

Several studies had examined how recommended monitoring is practiced in a clinical setting. However, no studies have examined metformin users specifically and variables that may be associated with suboptimal monitoring. The increasing diabetes population and lower safety awareness for metformin necessitates careful assessment of metformin safety laboratory screening. Therefore, we conducted this study to determine how the practice of laboratory monitoring for metformin reflects recommended guidelines. Also, patient characteristics that are potentially associated will be identified to highlight barriers to those safety measures. We hypothesize that lab monitoring for metformin will be suboptimal and may be associated with specific patient characteristics.

CHAPTER 2

METHODS

A cross-sectional observational study was performed using a claims database from a large commercial insurance plan. Data included members with diabetes and described members' membership status, demographic information, medical diagnosis, laboratory testing, medication dispensing, and healthcare utilization. The claims data included medical utilization data spanning from January 1, 2008 – May 31, 2010.

Inclusion criteria for the study population were a minimum of 18 years of age, diagnosed with diabetes according to ICD-9 code, having 18 months of continuous enrollment, and at least two metformin dispensing during the study frame. Also, patients were required to have three months before and after the study period to capture patients who may receive delayed annual lab monitoring. If members were hospitalized during the study period, they were excluded because all hospitalized patients would receive lab monitoring and therefore the results could be biased.

We hypothesized that laboratory monitoring for metformin

would be suboptimal and would vary according to patient characteristics. The main study outcome determined if metformin users with diabetes diagnosis received recommended safety lab monitoring for metformin. The manufacturer of metformin recommends that patients receive at least once yearly monitoring of glycosylated hemoglobin (A1C), anemia monitoring which includes either cell blood count (CBC) or vitamin B12 (B12) level, and serum creatinine level (SCR) which indicates patients' renal status. Members were considered to have optimal safety monitoring if they received all of the three lab tests.

The 2009 Healthcare Effectiveness Data and Information Set (HEDIS) standards and Current Procedure Terminology (CPT) codes served as a reference for identifying A1C, CBC, B12, and SCR from chemistry 7 tests. Common Procedural Terminology (CPT) codes were reviewed to identify any hospitalization and the number of clinic visits throughout the study period. The International Classification of Disease 9 (ICD 9) was used to confirm a diabetes diagnoses for each member and to identify comorbidities including cardiovascular disease, respiratory disease, mental disease, and renal disease. Cardiovascular disease included heart failure, hypertensive heart disease, myocardial infarction, angina, and atherosclerosis. Respiratory disease included

bronchitis, emphysema, asthma, and chronic obstructive pulmonary disease. Mental health disorders included bipolar, paranoid, psychosis, autism, personality disorder, depression, conduct disorder and attention deficit hyperactivity disorder. Lastly, renal disease included hypertensive chronic kidney disease, renovascular hypertension, cystic kidney disease, renal dysplasia, kidney transplant, renal dialysis, acute kidney failure, and glomerulonephritis.

Additionally, the frequencies of A1C, CBC, B12, SCR, and optimal lab monitoring performed were stratified into three different study periods: 12, 15, and 18 months. The frequency of each lab monitoring was to compare the difference among study length and allowing additional time of screening.

Descriptive statistics of the final cohort included age group, gender, diabetes medication use, comorbidities, and level of healthcare utilization. Diabetes medication use was classified according to the type of metformin product dispensed (sole ingredient vs. combination) and by insulin use. The comorbidities were classified as cardiovascular, respiratory, mental and renal diseases. Healthcare utilization measured five different components: the number of prescriptions dispensed during the baseline period (three months before the index date), the total cost of medication per month during

the screening period, the number of clinic visit and medication adherence rate throughout the study period. The frequencies of A1C, CBC, B12, SCR, and optimal monitoring performed were also measured in the final cohort. Descriptive statistics presented the frequencies and percentages for all variables assessed.

For these categorical variables, chi-square tests were performed to determine statistical significance of differences in proportions, according to the optimal lab monitoring outcome variables. These categories included age group, gender, types of diabetes medication use, comorbidities, and level of healthcare utilization. Multi-collinearity between these independent variables was examined by a correlation matrix and diagnostics, while the interaction among the independent variables was explored using multivariate logistic modeling.

Predictive models for optimal lab monitoring were built using multivariate logistic regression with a backward elimination process. All variables were first included and statistically insignificant independent variables ($P > 0.05$) were eliminated from the model step by step. The Hosmer-Lemshow goodness of fit test assessed the validity of the model. The significant independent variables in the

model were reported as an adjusted odds ratio with corresponding 95% confidence intervals.

Data analysis was performed using SAS (version 9.3).

CHAPTER 3

RESULTS

A total of 7068 members were selected from 14,908 members in the claims database (see flowchart). The sample population had a mean age of 63.1 years with a standard deviation of 12.16 (table 1). The distribution of age was highest in 40-64 year old group, 57.4 percent, and was second highest in the 65-79 year old group, 30.74 percent. The remaining age groups 18-39 year and 80 and older contributed 2.45 percent and 9.32 percent of the distribution, respectively. The percentages of male and female patients were 54.56 and 45.44 percent, respectively. A majority of members used metformin as a sole ingredient product, 84.80 percent. Only 19.95 percent of members were using insulin. The cohort members received average of 4.8 ± 2.94 prescriptions during three months before the study enrollment, and the median cost of the medication per month was \$20.64. The cohort members visited a doctor's office an average of 10.08 ± 6.19 times throughout the study. The average Medication Possession Rate (MPR) was 85.06 ± 20.82 percent.

During the 18 month study period, the recommended lab

monitoring for metformin such as HgbA1C testing, CBC, Vitamin B12, and Scr were performed in 75.44, 43.15, 10.98 and 52.57 percent of the cohort members. Members who received optimal monitoring (HgbA1c, CBC or B12, and Scr) were only 32.88 percent. The percent of optimal lab monitoring improved with longer period of assessment: 12 months 26.1%, 15 months 29.2% and 18 months 32.9% (table 2).

In the bivariate analyses, HgbA1C, Anemia Test (CBC or B12), Scr, and Optimal tests revealed statistically significant differences among age groups ($P < 0.0001$) (table 3). The patients in the oldest group were more likely to receive lab monitoring as compared with younger patients. Males received less frequent lab testing of any kind as compared with females (HgbA1C, Anemia Test, SCR, Optimal, respectively, $P < 0.0001$, $P < 0.0001$, $P = 0.0002$, $P < 0.0001$). Insulin-use was associated with greater frequency of HgbA1C testing, with statistically significant differences as compared to non-insulin-user ($P = 0.0254$). Patients with respiratory, cardiovascular, or renal disease were more likely to receive any type of lab monitoring performed as compared with patients not having these conditions. Unexpectedly, patients with mental health disorders had significantly higher number of optimal lab performed than patient without mental illnesses ($p = 0.0281$). All health utilization components demonstrated

statistically significant differences among different categories. A higher number of prescriptions and higher cost of medication at baseline and higher number of clinic visits were associated with increased lab monitoring. Medication adherence was also associated with frequent lab monitoring ($P < 0.0001$). Monitoring did not differ according to the type of metformin product utilized.

The logistic regression model for renal function testing revealed that age, cardiovascular disease, renal disease, number of clinic visits, and medication adherence were significant in fitting the prediction model (table 4). Patients in age category 4 (age 80 and over) were approximately four times more likely to receive serum creatinine testing as compared with those in age category 2 (40-65 year of age) (OR 4.007, 95%CI 3.292-4.877). Cardiovascular disease and renal disease also contributed to more frequent lab monitoring for metformin than patients with no such comorbidities. Patients with more than 14 clinic visits were almost 50 percent more likely to receive Scr testing than patients with 7-9 clinic visits (OR 1.489, CI95% 1.287-1.722). The variable for medication adherence was not significant in this analysis, and was thus excluded from the model.

The logistic regression model assessing anemia testing which reflected either a CBC or B12 test at least once yearly, included

gender as a significant independent variable (table 5). Unlike the other models, anemia testing was associated with gender. Female patients were 15 percent more likely to receive anemia tests than male patients (OR 1.151, 95%CI 1.042-1.270). Otherwise, this second model was similar to the previous model described above. Elderly people and patients with more frequent visit to clinic were also more likely to receive lab monitoring for anemia.

The model for HgbA1C testing included age, gender, insulin use, renal disease, and the number of clinic visits (table 6). The oldest age category was eight times more likely to receive HgbA1C testing than age category 2 (OR 8.283, 95%CI 5.816-11.797). Among the different labs for metformin, HgbA1C testing was most significantly associated with older age. HgbA1C testing was also associated with insulin use (OR 1.198, 95%CI 1.036-1.384).

Finally, the predictive logistic regression model for optimal monitoring performed included 7 variables: age group, cardiovascular disease, nephropathy, respiratory disease, mental health disorder, number of clinic visits, and medication adherence rate (table 7). No co-linearity was found between these independent variables, yet there was an interaction between category clinic visit3 (10-13) and respiratory disease. The interaction term was included in the model

originally because of its statistical significance with the outcome variable. However, ultimately, it was removed in a backward elimination step because the interaction term did not significantly affect the logistic model fit.

According to the final model, patients in age group of 65-80 year were 2 times more likely and those 80 year and over were 3 times more likely to receive optimal lab monitoring for metformin than age group of 40-65 year, odd ratios of 2.228 (95% CI 1.983-2.503) and 3.204 (95%CI 2.685-3.8230). When patients had other comorbid diseases such as cardiovascular disease, renal disease, respiratory disease or mental health disorders, such patients were more likely to receive optimal lab monitoring for metformin. The odd ratios of cardiovascular disease, renal disease, respiratory disease and mental disease were 1.190 (95% CI 1.053-1.344), 1.559 (95% CI 1.298-1.872), 1.205 (95% CI 1.040-1.396), and 1.194 (95% CI 1.030-1.384), respectively. In assessing level of health utilization, the cohort members who visited the clinic less than 6 times throughout a year were 23 percent less likely to receive optimal lab monitoring than members who visited 7-9 times (OR 0.774, 95%CI 0.667-0.898). The members who visited more than 14 times were 94 percent more likely

to receive optimal lab monitoring than members who visited 7-9 times (OR 1.935, CI95% 1.664-2.250). Lastly, patients who had a medication adherence rate of 0-69 percent were less likely to receive optimal care than patients who had adherence rate of 80-89 percent (OR 0.769, CI95% 0.617-0.957). As expected, higher medication adherence rate was associated with a greater frequency of optimal lab monitoring. Also, Hosmer and Lemeshow Goodness-of-Fit test reported a Chi-square of 6.4535; $p=0.5966$. There were no statistically significant differences between predictive and observed value, therefore, confirming the fitness of our modeling.

CHAPTER 4

DISCUSSION

Adverse drug events are unwanted effects from medications and many are preventable or treatable. A cohort study of Medicare enrollees conducted by Gurwitz JH et al in 2003 examined adverse events occurring in the ambulatory setting. The researcher reported that 27.6 percent of 1523 adverse drug events were preventable. Errors associated with adverse drug events occurred most commonly in the monitoring stage (60.8%), which was higher than errors of patient adherence (21%) or in prescribing stages (58.4%).¹⁴ In another study based on a systemic review of adverse medications events, Smith DH et al also reported that 21 percent of adverse events were preventable, with inadequate monitoring accountable for 45.4 percent of the drug therapy problems requiring hospital admission.¹⁵ Monitoring medication therapy is an important aspect of the patient care process and it is inadequately performed according to current literature.

This study examined the rate of optimal lab monitoring for metformin and attempted to identify the metformin users who are

more likely to receive appropriate safety monitoring. We failed to reject our stated hypothesis that monitoring in practice is suboptimal and associated with patient characteristics. The rate of lab monitoring for metformin was less frequent than clinically indicated, and varied according to patient characteristics. Only 32.9 percent of patients received optimal safety monitoring for metformin. The rate of HgbA1c, CBC, B12, and Scr tests, were 75.4%, 43.2%, 11.0%, and 52.6%, respectively. The creatinine monitoring rate was lower than previous literature has reported.^{12,13} This difference might be explained by the difference in data source, as Hurley et al used data from Health Maintenance Organizations (HMOs) having a larger number of observations and more complete information about patient care. Also, The Rabael et al study only looked at initial monitoring for metformin. Ongoing monitoring of metformin is expected to be less than initial monitoring. Interestingly, CBC rate was higher in our study members than other populations. The result might be caused by higher average age of our study patients compared with Hurley et al (63.1 vs. 57.8 year old).¹³

According to the bivariate analyses, all independent variables except type of diabetes medication use and the status of insulin use were associated with optimal lab monitoring performed. In addition,

multivariate logistic regression modeling revealed that several independent variables significantly impacted the performance of optimal monitoring. Those variables were age group, comorbidities, number of clinic visit and medication adherence rate.

The older age groups 65-80 year of age and 80 over were more likely to receive optimal safety monitoring while younger groups 40-65 were less likely. Cardiovascular disease, renal disease, mental disease, respiratory disease may have brought more attention from practitioners and revealed the association with higher possibility of optimal lab monitoring performed. In particular, patients with renal disease were 50 percent more likely to receive optimal care than patient without renal disease (OR 1.559, 95%CI 1.298 and 1.872). The group with 14 or more clinic visits was nearly twice as likely to receive optimal care as the group having 7-9 clinic visits. The patients with lower medication adherence rate than 70 were 23 percent less likely to have optimal monitoring than patients with an 80-89 percent adherence rate. High medication possession rate may represent high health awareness of patients (self-motivated) and be associated with more routine clinic visits.

Other multivariate models for Scr, CBC or B12, and HgbA1c were similarly affected by age, renal disease, and number of clinic

visits. Interestingly, gender was a statistically significant variable in the models assessing testing for CBC or B12 and HgbA1C. Females were more likely to receive an anemia test, given the higher prevalence of this condition in female patients. Yet, HgbA1C test cannot be explained by different disease prevalence, and it is uncertain why females appeared to receive indicated monitoring more frequently.

Overall, the recommended lab monitoring for metformin was not optimally executed in practice. The metformin users with diabetes were more likely to receive optimal lab monitoring if they were elderly with cardiovascular, renal, respiratory or mental disease, visited the clinic more than 14 times in a year and demonstrated a high adherence rate with medication. Conversely, healthcare providers have to focus on monitoring younger patients with fewer comorbidities who do not visit the clinic as often, and having lower adherence to medication. Such patients are easiest to be missed in care because healthcare encounters are infrequent and typically focus on acute medical needs. Recently, pharmacy lab monitoring alert systems and other interventions have been explored as a means to increase monitoring toward optimizing the safety of care.¹⁶ However, a first step is for healthcare providers to recognize that metformin lab

monitoring is suboptimal, and that relatively healthier patients may be more likely to miss required laboratory monitoring. Furthermore, it is important that providers recognize the importance of lab monitoring as an important process to promote safe medication use.

Several limitations of this study exist. First, the study was conducted in claims database that is specific to one disease state and the study period spanned only 18 months. It is not possible to generalize our results to larger populations, yet our sample represented typical diabetes patients using metformin. Secondly, the all-or-none approach to our assessment of optimal lab monitoring performed may be overly strict considering typical medical practice. Recommended monitoring for metformin may be overly excessive and impossible to implement. Third, the study data have particular limitations. The claims database was compiled based on the paid claims. Therefore, any diagnosis, procedure, and pharmacy data that was not recorded or paid out-of-pocket was missed. Also, the results could have been biased by patients' other comorbidities or medications that can influence prescribers to order labs. In this study, we examined interaction with comorbidities and age to account for this bias.

Some may argue that another limitation to this study is the fact

that metformin is considered to be very safe pharmacotherapy. For example, several literature has been published that rebukes the association of lactic acidosis with metformin use^{17, 18}. However, monitoring guidelines and recommendations should ideally match practice regardless of the perceived degree of the true risk. In general, patients are all at risk of taking medication and usually risks are unknown. Therefore, healthcare providers must follow the guidelines for safety monitoring to protect their patients, even though it might feel unnecessary or ineffective. The roles of government and researchers are to make a precise and practical guideline for periodic medication safety lab monitoring. Everyone together should make every effort to protect patients from harm and prevent unnecessary hospitalization and death.

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FIGURE 1
SAMPLE SELECTION FLOWCHART

TABLES

Table 1: Characteristics of the Study Sample

Variable	Cohort (n=7068)
Age, years	
Mean	63.1±12.2 (18 - 99)
18 - 39	173 (2.45%)
40 – 64	4063 (57.48%)
65 – 79	2173 (30.74%)
80 and more	659 (9.32%)
Gender	
Male	3856 (54.56%)
Female	3212 (45.44%)
Diabetes Medication Use	
Metformin Mono-product	5994 (84.80%)
Metformin Combination Product	1074 (15.20%)
Insulin Dependent(Use)	1410 (19.95%)
Insulin Independent(No Use)	5658 (80.05%)
Co-morbidity	
Respiratory	981 (13.88%)
Cardiovascular	1753 (24.80%)
Mental Health Disorder	1038 (14.69%)
Nephropathy	568 (8.04%)
Healthcare Utilization	
Number of Prescriptions at Baseline (Three months period before the index date)	
Mean	4.8±2.94 (1 – 28)
0 – 2	1636 (23.15%)
3	1111 (15.72%)
4 – 5	1928 (27.28%)
6 – 28	2393 (33.86%)
Total Cost of Medications Per Month	
Median(Dollar \$)	20.64 (0 - 538.83)
0 – 5.2	1769 (25.03%)
5.3 – 11.7	1773 (25.08%)

Table 1: Characteristics of the Study Sample Continued	
11.8 – 26.7	1769 (25.03%)
26.8 – 538.8	1757 (24.86%)
Number of Clinic Visit During the Study Period (During 18 months)	
Mean	10.08±6.19 (0 – 76)
0 – 6	2201 (31.14%)
7 – 9	1718 (24.31%)
10 – 13	1580 (22.35%)
14- 76	1569 (22.20%)
Level of Adherence (Medication Possession Rate %)	
Mean	85.06±20.82 (5 – 100%)
90 – 100	4420 (62.54%)
80 – 89	547 (7.53%)
70 – 79	532 (7.63%)
0 – 69	1569 (22.20%)
Lab Monitoring(During 18 months)	
A1C	5332 (75.44%)
CBC	3050 (43.15%)
B12	776 (10.98%)
Renal Screening (Scr)	3716 (52.57%)
Optimal*	2324 (32.88%)

Optimal* recommend lab monitoring for metformin is to complete HgbA1C, CBC or B12, and renal function test (SCR) annually.

Table 2: Frequency of Laboratory Monitoring Performed Based According to 12, 15, and 18 Month Intervals

	12 Months	15 Months	18 Months
Optimal Lab	1841 (26.1%)	2067 (29.2%)	2324 (32.9%)
HgbA1C	5072 (71.8%)	5201 (73.6%)	5332 (75.4%)
CBC	2561 (36.2%)	2810 (39.8%)	3050 (43.2%)
B12	606 (8.6%)	683 (9.7%)	776 (11.0%)
SCR	3304 (46.8%)	3490 (49.4%)	3716 (52.6%)

Table 3: Performance of Recommended Laboratory Monitoring During the 12 Month Study Period According to Patient Characteristics.

Variable	Hgb A1C testing (n=5332)	CBC or B12 Testing (Anemia Test) (n=3233)	Renal Function Test (Scr) (n=3716)	Optimal* Monitoring Performed (n=2324)
	N (%)	N (%)	N (%)	N (%)
Age, years				
18-39	121 (2.3%)	65 (2%)	63 (1.7%)	38 (1.6%)
40-64	2734 (51.3%)	1500 (46.4%)	1715 (46.2%)	981 (42.2%)
65-79	1852 (34.7%)	1227 (38%)	1431 (38.5%)	952 (41%)
80 and more	625 (11.7%)	441 (13.6%)	507 (13.6%)	353 (15.2%)
	P<0.0001	P<0.0001	P<0.0001	P<0.0001
Gender				
Male	2817 (52.8%)	1649 (51%)	1949 (52.4%)	1191 (51.2%)
Female	2515 (47.2%)	1584 (49%)	1767 (47.6%)	1133 (48.8%)
	P<0.0001	P<0.0001	P=0.0002	P<0.0001
Diabetes Medication Use				
Metformin Mono-product	4517 (84.7%)	2735 (84.6%)	3140 (84.5%)	1957 (84.2%)
Combination product	815 (15.3%)	498 (15.4%)	576 (15.5%)	367 (15.8%)
	P=0.7124	P=0.6541	P=0.4516	P=0.3282
Insulin Dependent(Use)	1096 (20.6%)	645 (20%)	765 (20.6%)	485 (20.9%)
Independent (No Use)	4236 (79.4%)	2588 (80%)	2951 (79.4%)	1839 (79.1%)
	P=0.0254	P=0.9978	P=0.1579	P=0.1755
Co-morbidity*				
Respiratory	768 (14.4%)	515 (16%)	589 (15.9%)	407 (17.5%)
	P=0.0255	P<0.0001	P<0.0001	P<0.0001
Cardiovascular	1423 (26.7%)	949 (29.4%)	1109 (29.8%)	753 (32.4%)
	P<0.0001	P<0.0001	P<0.0001	P<0.0001

Table 3: Performance of Recommended Laboratory Monitoring During the 12 Month Study Period According to Patient Characteristics. Continued				
Mental Disease	767 (14.4%)	499 (15.4%)	554 (14.9%)	372 (16%)
	P=0.2101	P=0.1025	P=0.5778	P=0.0281
Nephropathy	480 (9%)	351 (10.9%)	386 (10.4%)	279 (12%)
	P<0.0001	P<0.0001	P<0.0001	P<0.001
Health Utilization				
Number of Prescriptions at Baseline (Three months period before the index date)				
0 – 2	1199 (22.5%)	679 (21%)	815 (22%)	462 (19.9%)
3	796 (14.9%)	451 (14%)	541 (14.6%)	314 (13.5%)
4 – 5	1482 (27.8%)	895 (27.7%)	1013 (27.3%)	640 (27.5%)
6 – 28	1855 (34.8%)	1208 (37.4%)	1347 (36.2%)	908 (39.1%)
	P=0.0001	P<0.0001	P<0.0001	P<0.0001
Total Cost of Medications Per Month				
\$0 – 5.2	1250 (23.4%)	722 (22.3%)	838 (22.6%)	497 (21.4%)
\$5.3 – 11.7	1350 (25.3%)	784 (24.2%)	956 (25.7%)	574 (24.7%)
\$11.8 – 26.7	1354 (25.4%)	855 (26.4%)	957 (25.8%)	619 (26.6%)
\$26.8 – 538.8	1378 (25.8%)	872 (27%)	965 (26%)	634 (27.3%)
	P<0.0001	P<0.0001	P<0.0001	P<0.0001
Number of Clinic Visit During the Study Period (During 18 months)				
0 – 6	1480 (27.8%)	770 (23.8%)	914 (24.6%)	495 (21.3%)
7 – 9	1309 (24.5%)	743 (23%)	883 (23.8%)	499 (21.5%)
10 – 13	1277 (24%)	801 (24.8%)	931 (25.1%)	599 (25.8%)
14- 76	1266 (23.7%)	919 (28.4%)	988 (26.6%)	731 (31.5%)
	P<0.0001	P<0.0001	P<0.0001	P<0.0001
Level of Adherence (Medication Possession Rate %)				
90 – 100	3429 (64.3%)	2111 (65.3%)	2457 (66.1%)	1545 (66.5%)
80 – 89	395 (7.4%)	252 (7.8%)	274 (7.4%)	185 (8%)
70 – 79	382 (7.2%)	209 (6.4%)	252 (6.8%)	157(6.8%)
0 – 69	1126 (21.1%)	661 (20.4%)	733 (19.7%)	437 (18.8%)
	P<0.0001	P<0.0001	P<0.0001	P<0.0001

*P-value according to the chi-square test.

Table 4: Results of Predictive Logistic Modeling: Adjusted Odds Ratios for SCR Testing According to Patient Characteristics

	Beta	Adjusted Odds Ratios	95% CI Low	95% CI High
Age				
Cat 1	-0.1891	0.828	0.600	1.141
Cat 2	N/A	N/A		
Cat 3	0.8698	2.386	2.134	2.688
Cat 4	1.3880	4.007	3.292	4.877
Comorbidity				
Cardio-Disease	0.1837	1.202	1.065	1.356
Nephropathy	0.4101	1.507	1.242	1.828
Health Utilization				
Clinic Visit1	-0.3317	0.718	0.629	0.819
Clinic Viist2	N/A	N/A		
Clinic Visit3	0.2537	1.289	1.117	1.487
Clinic Viist4	0.3979	1.489	1.287	1.722
Medication Adherence Level				
MPR1	0.0882	1.092	0.906	1.316
MPR2	N/A	N/A		
MPR3	-0.1003	0.905	0.704	1.161
MPR4	-0.0848	0.919	0.749	1.127

Table 5: Results of Predictive Logistic Modeling: Adjusted Odds Ratios for CBC or B12 Testing According to Patient Characteristics

	Beta	Odd Ratios	95% CI Low	95% CI High
Age				
Cat 1	0.0104	1.010	0.734	1.391
Cat 2	N/A	N/A		
Cat 3	0.7276	2.070	1.858	2.306
Cat 4	1.1387	3.123	2.612	3.733
Gender				
Female	0.1402	1.151	1.042	1.270
Comorbidity				
Nephropathy	0.4101	1.507	1.242	1.828
Health Utilization				
Clinic Visit1	-0.2918	0.747	0.654	0.853
Clinic Visit2	N/A	N/A		
Clinic Visit3	0.2525	1.287	1.118	1.482
Clinic Visit4	0.5609	1.752	1.519	2.021

Table 6: Results of Predictive Logistic Modeling: Adjusted Odds Ratios for HgbA1C Testing According to Patient Characteristics

	Beta	Odd Ratios	95% CI Low	95% CI High
Age				
Cat 1	0.1077	1.114	0.796	1.558
Cat 2	N/A	N/A		
Cat 3	0.9795	2.663	2.323	3.054
Cat 4	2.1142	8.283	5.816	11.797
Gender				
Female	0.1352	1.145	1.020	1.285
Insulin Use				
Insulin Use	0.1803	1.198	1.036	1.384
Comorbidity				
Nephropathy	0.3207	1.378	1.080	1.758
Health Utilization				
Clinic Visit1	-0.3865	0.679	0.587	0.787
Clinic Visit2	N/A	N/A		
Clinic Visit3	0.2094	1.233	1.038	1.465
Clinic Visit4	0.1677	1.183	0.995	1.406

Table 7: Results of Predictive Logistic Modeling: Adjusted Odds Ratios for Optimal Testing According to Patient Characteristics

	Beta	Odd Ratios	95% CI Low	95% CI High
Age				
Cat 1	-0.0939	0.910	0.625	1.326
Cat 2	N/A	N/A		
Cat 3	0.8010	2.228	1.983	2.503
Cat 4	1.1644	3.204	2.685	3.823
Comorbidity				
Cardio-Disease	0.1738	1.190	1.053	1.344
Nephropathy	0.4439	1.559	1.298	1.872
Respiratory	0.1865	1.205	1.040	1.396
Mental Disease	0.1775	1.194	1.030	1.384
Health Utilization				
Clinic Visit1	-0.2568	0.774	0.667	0.898
Clinic Visit2	N/A	N/A		
Clinic Visit3	0.3430	1.409	1.212	1.638
Clinic Visit4	0.6602	1.935	1.664	2.250
Medication Adherence Level				
MPR1	-0.0982	0.906	0.744	1.104
MPR2	N/A	N/A		
MPR3	-0.2077	0.812	0.621	1.063
MPR4	-0.2633	0.769	0.617	0.957

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