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Survival Data Mining: Treatment of Chronic Illness

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ABSTRACT

Patients with chronic illness often have many medications available for treatment. Medications are changed, and added when the patient experiences side effects or the disease progresses so that a medication is no longer effective. It is the purpose of this project to use survival data mining techniques to investigate prescribed medications for patients with Type II diabetes.

We examine the Medical Expenditure Panel Survey for the years 2000-2004 and validate the results using a second database for a cohort of patients with diabetes. We preprocess the data by filtering to medications listed for the ICD9 code for diabetes. Then we remove medications not specifically related to glucose control, eliminating misspellings and name variations. In the MEPS database, this leaves a total of 73,000 prescriptions. We use sequential market basket analysis to examine combinations of medications used. We also use survival data mining techniques since medication switching is quite similar to a customer switching to a new provider. Since switching can occur multiple times, there are multiple time points to investigate.

A total of 30% of the prescriptions were for insulin, with 24% for Metformin. Most of the switching from one drug to another occurred within five months or less. Changing and adding medications tends to occur within short periods of time. In addition, it appears to be far more common to switch medications rather than to add. Also, patients averaged 9 prescriptions each, when 12 prescriptions (30 days each) indicates compliance.

INTRODUCTION

There are developed guidelines that suggest optimal treatments for patients with chronic diseases. Generally, chronic diseases require multiple decisions concerning medications. However, it is rare to examine decisions in sequence; the assumption is often made that decisions are independent of one another.

In this project, we investigate sequential decision making for patients with diabetes. Diabetes mellitus is a progressive, degenerative disease that requires regular monitoring and medication adjustments, including adding medications and dose adjustments throughout the life of the patient. Guidelines suggest that medications should be prescribed depending upon the results of an A1C lab test. If one medication is not controlling glucose values, a second or even a third medication should be added before starting the patient on insulin. However, the prescription databases examined show that patients are far more likely to switch medications than to add. In addition, the use of A1C lab tests are not in common use.

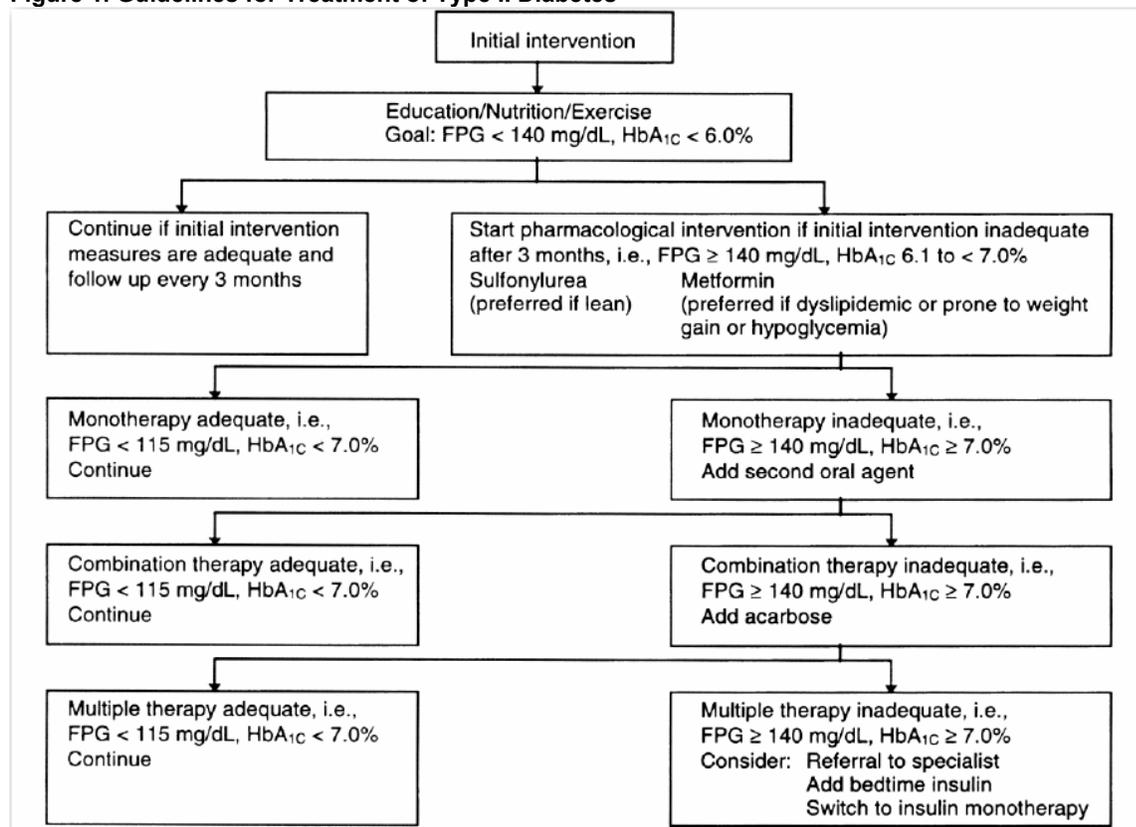
BACKGROUND

There are a number of different types of medications used to treat Type II diabetes. The oldest drugs, called sulfonylureas (Tolbutamide, Acetohexamide, Tolazamide, and Chlorpropamide) lower blood glucose levels by increasing the release of insulin from the pancreas. More recent drugs in this group are Glyburide, Glipizide, and Glimepiride. The next group developed, called biguanides, is primarily represented by Metformin (Glucophage). It decreases the amount of glucose produced by the liver, and patients usually do not have problems with hypoglycemia (low blood sugar) when taking this medication. The class called thiazolidinediones (Proglitazone and rosiglitazone) lowers blood glucose by improving the sensitivity of cells to insulin. Precose works on the intestine by blocking the absorption of sugar and works best in combination with other medications. Starlix (Nateglinide) and Prandin (repaglinide) can be added to lower postprandial blood glucose (after eating) in monotherapy with Metformin or the glitazones.

More recently, there are injectable medications and inhaled insulins. Also, some combination medications are available, combining Glyburide (Glucovance), Pioglitazone, Glipizide, or Rosiglitazone with Metformin. When these medications become ineffective (as the diabetes progresses), insulin can be added to the treatment, or insulin used alone.

We first look at the research literature to see if there are established guidelines for prescribing these medications for Type II diabetes, and whether actual treatment corresponds to these guidelines. One such attempt at a guideline was developed at a forum in Dallas, Texas in 1997.¹ Figure 1 gives a diagram of the results of that forum.

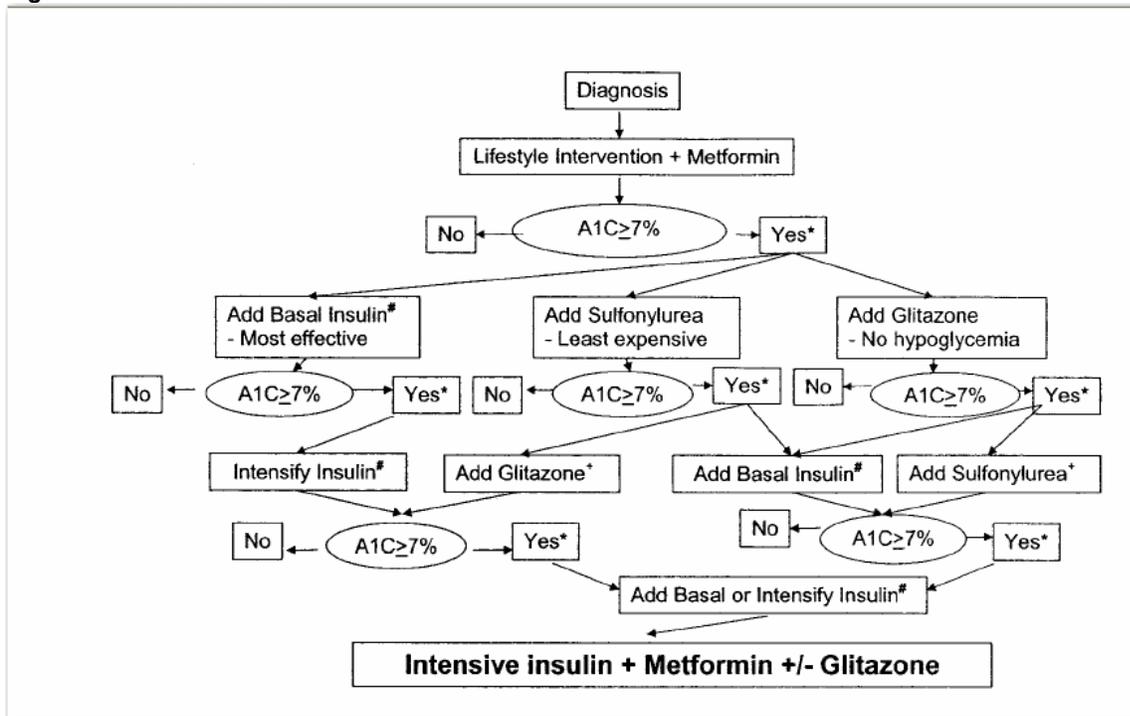
Figure 1. Guidelines for Treatment of Type II Diabetes



Note that the first recommended drug treatment is with Metformin, or one of the sulfonylurea medications (with no indication as to which one). The second recommendation is to add a second oral agent, again without indication of which one. The third intervention is to add acarbose (Precose). If a combination of the three drugs does not control the glucose levels as measured by the Hemoglobin A1C test with control identified as less than 7% A1C, then insulin is recommended, either at bedtime in combination with the other medications or insulin only. As an alternate to the A1C test, a fasting glucose test can be used. Therefore, these recommendations still leave considerable room for physician discretion in the choice of medications. In addition, these guidelines were published in 1997. Since then, an inhaled insulin (Exubera) was approved for use. There have been additional medications as well introduced since that date. These guidelines allow for the use of either fasting glucose or the A1C for decision making.

Figure 2 shows the guidelines adopted by the American Diabetes Association in 2007. Again, the emphasis is on adding medications to improve control rather than switching. These guidelines suggest starting with Metformin as the first medication. In addition, the guidelines have moved to the use of the A1C test exclusively for decision making with respect to treatments.² A fasting glucose test is no longer sufficient.

Figure 2. ADA Guidelines



The patient costs of medication therapy are also related to patient compliance with use, which can be low.³⁻⁵ One recent study showed that the availability of a treatment protocol resulted in more aggressive use of medications by physicians, and better glucose control by patients.⁶ Physicians also increase the number of medications to attempt to establish glucose control, switching to insulin reluctantly.⁷ Patients, too, have a reluctance to switch to insulin because it must be administered by injection.⁸

There are, however, few studies that directly compare different treatment combinations, and the impact of switching or adding medications.⁹ Studies have shown that physician decisions concerning the use of these medications can vary with the cognitive functioning of the patient.¹⁰ They also differ by physician specialty and geographic region of practice.¹¹ Another item to consider is the reliance on the A1C test to direct treatment if the desired value of 7% is not reached. Do physicians base their treatment decisions on the test? Therefore, we will also consider the relationship of the A1C test to the prescribing of medications.

METHOD

The MEPS dataset has prescriptions for a cohort of approximately 30,000 people for the years 2000-2004, the latest year available. The dataset can be found at <http://www.meps.ahrq.gov/mepsweb/>. We want to examine the use of medications for Type II diabetes, filtering down to the medications typically prescribed for diabetes. This yields a total of 73,000+ prescriptions, with multiple prescriptions per individual in the dataset.

First, we take advantage of the procedures available in SAS Text Miner. We create text strings of all prescriptions per patient, changing the observational unit from medication prescribed to patient. We create these text strings by first transposing the prescription name and then by concatenating the transposed columns. We use the code:

```

proc sort data = sasuser.Patidandmedicationsonly out= work.sort_out;
  by duid rxname;
run;
options obs=max;
data work.sort_out1;
  set work.sort_out;
  rxname = translate(left(trim(rxname)),'_',' ');
run;
proc Transpose data=work.sort_out1
  out=work.tran 7*(drop=_name_ _label_) */
  prefix=med_;

```

```

var rxname ;
by duid;
run;
data sasuser.concat( keep= duid rxname ) ;
  length rxname $32767 ;
  set work.tran ;
  array rxconcat med : ;
  rxname = left( trim( med_1 ) ) ;
  do i = 2 to dim( rxconcat ) ;
    rxname = left(trim(rxname)) || ' ' || left(trim( rxconcat[i] ) ) ;
  end ;
run ;

```

Then we use the term list defined in Text Miner to find the total number of prescriptions, and the number of different patients with prescriptions (Table 1). For example, there are a total of 17,697 prescriptions for the drug, Metformin for 1985 patients for an average of almost 9 prescriptions per patient (which can include refills). Since most medications are dispensed as a 30-day supply, there should be 12 prescriptions per patient.

Text Miner can routinely examine the difference between the number of prescriptions and the number of patients. It is a quick way to examine prescriptions when there are many options available for prescribing to patients.

Next, we examine the data using market basket analysis. This technique enables us to investigate switching from one medication to another. If we define prescription dates sequentially, we can also examine the order in which different medications were prescribed. We should note that inferential statistics and p-values have little importance when investigating datasets with so many observations. In addition, our interest here is to investigate the decision making process and the sequence of decisions. Although we can generate a hypothesis of the form:

$$\begin{aligned}
 H_0: P_{\text{switching from A}} &= P_{\text{switching from B}} \\
 H_1: P_{\text{switching from A}} &\neq P_{\text{switching from B}}
 \end{aligned}$$

and the results will be highly statistically significant, it is more important to investigate the reasons these proportions are different.

The third major technique we will use is that of survival data mining. This technique will enable us to drill down into details to determine whether patients are adding medications or just switching. In addition, we will examine the relationship of the A1C testing to changes in medications.

RESULTS FROM MEPS

We first look at the number of prescriptions (by patient) for each of the medications. As the latest available data are from 2004, more recently developed medications will not appear in the database. Table 1 lists the prescriptions.

Table 1. Prescriptions by Patient for Diabetes Medications

| Medication | Number of Prescriptions | Number of Patients |
|-------------------------|-------------------------|--------------------|
| Metformin | 17,697 | 1985 |
| Insulin | 22,347 | 1677 |
| Glipizide | 9119 | 963 |
| Glyburide | 8055 | 943 |
| Rosiglitazone | 4350 | 583 |
| Ploglitazone | 3827 | 524 |
| Glimepiride | 3572 | 413 |
| Glucovance | 2779 | 336 |
| Metformin-rosiglitazone | 393 | 85 |
| Starlix | 330 | 55 |
| Prandin | 330 | 53 |
| Glyburide-metformin | 145 | 35 |
| Precose | 148 | 23 |
| Chlorpropamide | 132 | 17 |
| Glyset | 114 | 14 |
| Tolbutamide | 22 | 2 |

We also examine prescriptions for patients with and without insulin (Tables 2 and 3 respectively). Table 2 does

suggest that many of the patients taking Insulin are also taking other medications since all of the text strings filtered here include at least one prescription of Insulin. Many of these patients will have Type I diabetes. Display 1 shows how medications can be filtered using Text Miner (Display 1), restricting the list to patients who have some Insulin prescriptions.

Display 1. Filtering in Text Miner for Those Prescribed Insulin

The screenshot shows a 'Build Where Clause' dialog box. It contains a table with three columns: 'Column name:', 'Operator', and 'Value'. The 'Column name:' field contains '(DRUG)', the 'Operator' field contains 'not Contains', and the 'Value' field contains 'Insulin'. Below the table are three buttons: 'Add', 'Custom', and 'Delete'. At the bottom right are three buttons: 'OK', 'Cancel', and 'Help'.

Table 2. Prescriptions by Patients Also Prescribed Insulin

| Medication | Number of Prescriptions | Number of Patients |
|-------------------------|-------------------------|--------------------|
| Insulin | 22,347 | 1677 |
| Metformin | 3809 | 424 |
| Rosiglitazone | 1445 | 190 |
| Glipizide | 1454 | 164 |
| Glyburide | 1146 | 160 |
| Ploglitazone | 1149 | 157 |
| Glimepiride | 809 | 92 |
| Glucovance | 648 | 75 |
| Prandin | 88 | 15 |
| Starlix | 81 | 15 |
| Prandin | 330 | 53 |
| Metformin-rosiglitazone | 60 | 14 |
| Precose | 44 | 12 |
| Gluburide-metformin | 28 | 6 |
| Glyset | 41 | 5 |
| Chlorpropamide | 22 | 1 |
| Tolbutamide | 6 | 1 |

Table 3. Prescriptions by Patients Not Prescribed Insulin

| Medication | Number of Prescriptions | Number of Patients |
|-------------------------|-------------------------|--------------------|
| Metformin | 13,888 | 1561 |
| Glipizide | 7665 | 799 |
| Glyburide | 6909 | 783 |
| Rosiglitazone | 2905 | 393 |
| Plotlitazone | 2678 | 367 |
| Glimepiride | 2763 | 321 |
| Glucovance | 2131 | 261 |
| Metformin-rosiglitazone | 333 | 71 |
| Starlix | 249 | 40 |
| Prandin | 242 | 38 |
| Glyburide-metformin | 117 | 29 |
| Chlorpropamide | 110 | 16 |
| Glyset | 73 | 11 |
| Precose | 104 | 11 |

| Medication | Number of Prescriptions | Number of Patients |
|-------------|-------------------------|--------------------|
| Tolbutamide | 16 | 1 |

The most popular medication appears to be Metformin either by itself, or as part of a combination drug. However, at this point, we have nothing to identify switching from one medication to another. To examine this issue, we use market basket analysis.

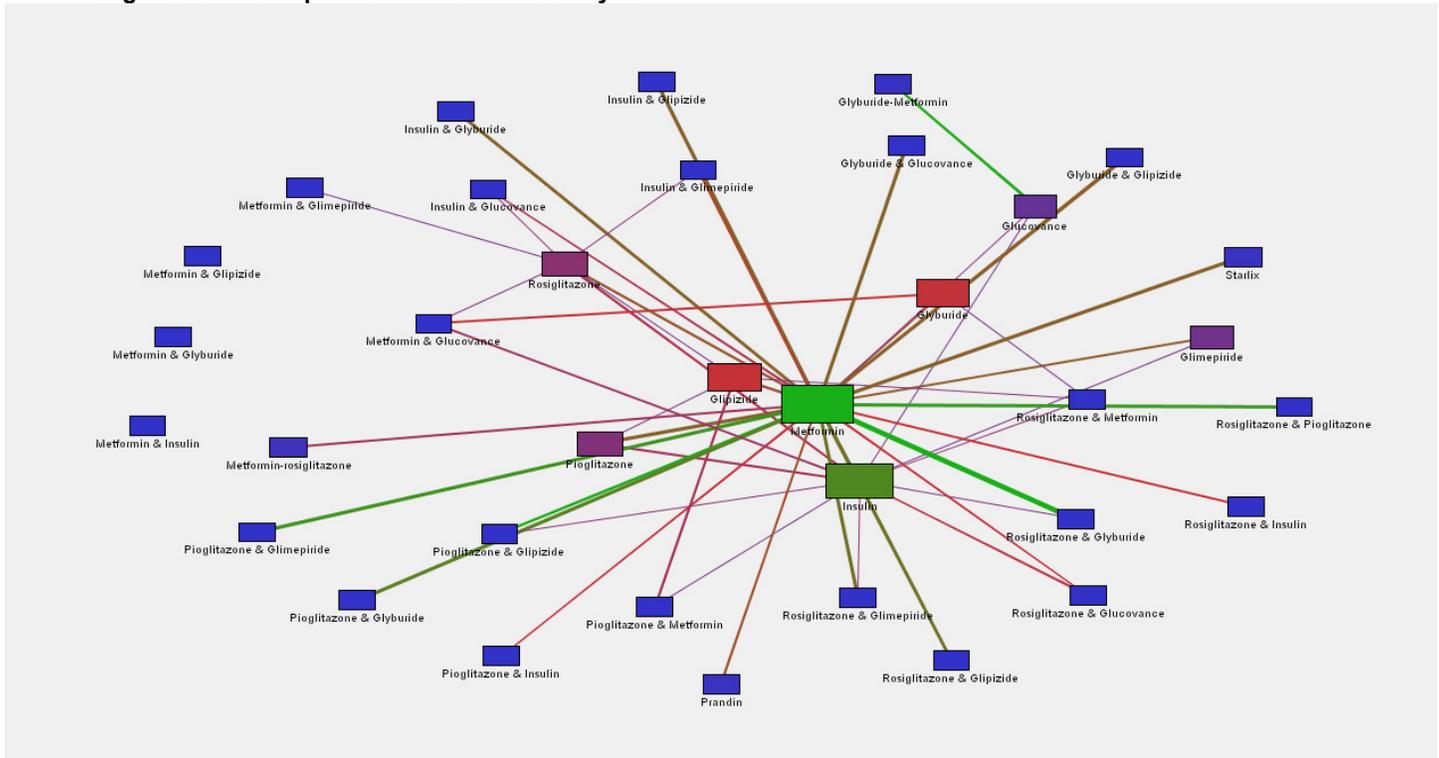
Although we are primarily interested in the sequencing of drug A to drug B, most of the medications listed in the dataset do not have accompanying dates. Eliminating all records without dates drastically reduces the dataset. Therefore, we first look to the dataset without sequencing. The rules with the highest transaction count are listed in Display 2 with the corresponding link graph in Figure 3.

Display 2. Rules Table for Market Basket Analysis

| Relations | Expected C... | Confidence(...) | Support(%) | Lift | Transaction... | Rule |
|-----------|---------------|-----------------|------------|------|----------------|--|
| 2 | 36.02 | 21.36 | 9.11 | 0.59 | 424.00 | Metformin ==> Insulin |
| 2 | 42.63 | 25.28 | 9.11 | 0.59 | 424.00 | Insulin ==> Metformin |
| 2 | 20.68 | 21.06 | 8.98 | 1.02 | 418.00 | Metformin ==> Glipizide |
| 2 | 42.63 | 43.41 | 8.98 | 1.02 | 418.00 | Glipizide ==> Metformin |
| 2 | 20.25 | 20.00 | 8.53 | 0.99 | 397.00 | Metformin ==> Glyburide |
| 2 | 42.63 | 42.10 | 8.53 | 0.99 | 397.00 | Glyburide ==> Metformin |
| 2 | 42.63 | 44.43 | 5.56 | 1.04 | 259.00 | Rosiglitazone ==> Metformin |
| 2 | 12.52 | 13.05 | 5.56 | 1.04 | 259.00 | Metformin ==> Rosiglitazone |
| 2 | 42.63 | 47.14 | 5.30 | 1.11 | 247.00 | Pioglitazone ==> Metformin |
| 2 | 11.25 | 12.44 | 5.30 | 1.11 | 247.00 | Metformin ==> Pioglitazone |
| 2 | 36.02 | 32.59 | 4.08 | 0.90 | 190.00 | Rosiglitazone ==> Insulin |
| 2 | 42.63 | 46.00 | 4.08 | 1.08 | 190.00 | Glimepiride ==> Metformin |
| 2 | 12.52 | 11.33 | 4.08 | 0.90 | 190.00 | Insulin ==> Rosiglitazone |
| 2 | 36.02 | 17.03 | 3.52 | 0.47 | 164.00 | Glipizide ==> Insulin |
| 2 | 36.02 | 16.97 | 3.44 | 0.47 | 160.00 | Glyburide ==> Insulin |
| 2 | 36.02 | 29.96 | 3.37 | 0.83 | 157.00 | Pioglitazone ==> Insulin |
| 2 | 20.68 | 21.61 | 2.71 | 1.04 | 126.00 | Rosiglitazone ==> Glipizide |
| 2 | 12.52 | 13.08 | 2.71 | 1.04 | 126.00 | Glipizide ==> Rosiglitazone |
| 2 | 20.68 | 22.90 | 2.58 | 1.11 | 120.00 | Pioglitazone ==> Glipizide |
| 2 | 11.25 | 12.46 | 2.58 | 1.11 | 120.00 | Glipizide ==> Pioglitazone |
| 2 | 36.02 | 22.28 | 1.98 | 0.62 | 92.00 | Glimepiride ==> Insulin |
| 2 | 20.25 | 15.27 | 1.91 | 0.75 | 89.00 | Rosiglitazone ==> Glyburide |
| 2 | 20.25 | 16.60 | 1.87 | 0.82 | 87.00 | Pioglitazone ==> Glyburide |
| 2 | 8.87 | 14.24 | 1.78 | 1.60 | 83.00 | Rosiglitazone ==> Glimepiride |
| 2 | 42.63 | 24.70 | 1.78 | 0.58 | 83.00 | Glucovance ==> Metformin |
| 2 | 12.52 | 20.10 | 1.78 | 1.60 | 83.00 | Glimepiride ==> Rosiglitazone |
| 3 | 20.68 | 18.40 | 1.68 | 0.89 | 78.00 | Metformin & Insulin ==> Glipizide |
| 3 | 36.02 | 18.66 | 1.68 | 0.52 | 78.00 | Metformin & Glipizide ==> Insulin |
| 3 | 42.63 | 47.56 | 1.68 | 1.12 | 78.00 | Insulin & Glipizide ==> Metformin |
| 3 | 20.68 | 30.77 | 1.63 | 1.49 | 76.00 | Pioglitazone & Metformin ==> Glipizide |
| 3 | 20.25 | 17.92 | 1.63 | 0.89 | 76.00 | Metformin & Insulin ==> Glyburide |
| 3 | 36.02 | 19.14 | 1.63 | 0.53 | 76.00 | Metformin & Glyburide ==> Insulin |
| 3 | 42.63 | 63.33 | 1.63 | 1.49 | 76.00 | Pioglitazone & Glipizide ==> Metformin |
| 3 | 42.63 | 47.50 | 1.63 | 1.11 | 76.00 | Insulin & Glyburide ==> Metformin |
| 3 | 8.98 | 14.50 | 1.63 | 1.62 | 76.00 | Pioglitazone ==> Metformin & Glipizide |
| 3 | 11.25 | 18.18 | 1.63 | 1.62 | 76.00 | Metformin & Glipizide ==> Pioglitazone |
| 2 | 36.02 | 22.32 | 1.61 | 0.62 | 75.00 | Glucovance ==> Insulin |
| 3 | 36.02 | 26.64 | 1.48 | 0.74 | 69.00 | Rosiglitazone & Metformin ==> Insulin |
| 3 | 42.63 | 36.32 | 1.48 | 0.85 | 69.00 | Rosiglitazone & Insulin ==> Metformin |

Because of the high number of prescriptions for Metformin, many of the rules include a switch to or from Metformin; fewer include a switch to or from Insulin. The highest transaction counts include Metformin.

Figure 3. Link Graph for Market Basket Analysis



The link graph shows Metformin, Insulin, and Glipizide at the center with Glyburide close by, and the rest of the medications spoking out from the center. It indicates that these four drugs are those in primary use with the rest added, or substituted for the other medications.

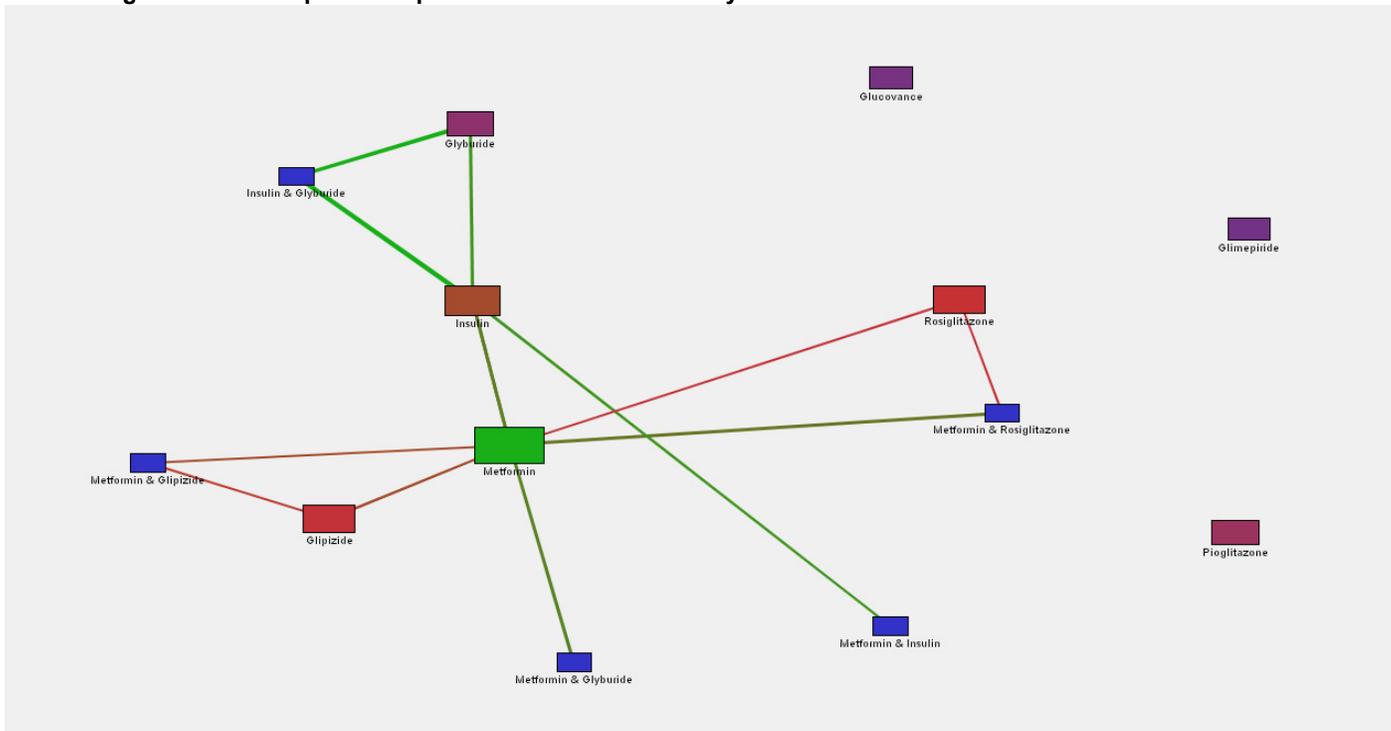
Once we filter out all medications without a date, the number of prescriptions is reduced to 2700+. Display 3 and Figure 4 show the results of a sequential market basket analysis.

Display 3. Rules Table for Sequential Market Basket Analysis

| Transaction... | Support(%) | Confidence(...) | Rule | Chain Item 1 | Chain Item 2 | Chain Item 3 |
|----------------|------------|-----------------|------------------------|---------------------------|---------------|---------------|
| 2 | 181 | 19.38 | 56.92Metformin ==... | Metformin | Metformin | |
| 2 | 127 | 13.60 | 66.49Insulin ==> In... | Insulin | Insulin | |
| 3 | 93 | 9.96 | 51.38Metformin ==... | Metformin | Metformin | Metformin |
| 3 | 84 | 8.99 | 66.14Insulin ==> In... | Insulin | Insulin | Insulin |
| 2 | 81 | 8.67 | 51.92Rosiglitazone... | Rosiglitazone | Rosiglitazone | |
| 2 | 80 | 8.57 | 52.63Glipizide ==> ... | Glipizide | Glipizide | |
| 2 | 53 | 5.67 | 55.21Glyburide ==... | Glyburide | Glyburide | |
| 2 | 49 | 5.25 | 43.75Pioglitazone ... | Pioglitazone | Pioglitazone | |
| 3 | 46 | 4.93 | 57.50Glipizide ==> ... | Glipizide | Glipizide | Glipizide |
| 3 | 46 | 4.93 | 56.79Rosiglitazone... | Rosiglitazone | Rosiglitazone | Rosiglitazone |
| 2 | 38 | 4.07 | 52.05Glucovance ... | Glucovance | Glucovance | |
| 2 | 36 | 3.85 | 52.17Glimepiride =... | Glimepiride | Glimepiride | |
| 3 | 29 | 3.10 | 54.72Glyburide ==... | Glyburide | Glyburide | Glyburide |
| 3 | 23 | 2.46 | 60.53Glucovance ... | Glucovance | Glucovance | Glucovance |
| 3 | 22 | 2.36 | 61.11Glimepiride =... | Glimepiride | Glimepiride | Glimepiride |
| 3 | 22 | 2.36 | 44.90Pioglitazone ... | Pioglitazone | Pioglitazone | Pioglitazone |
| 2 | 21 | 2.25 | 6.60Metformin ==... | Metformin | Glipizide | |
| 2 | 20 | 2.14 | 12.82Rosiglitazone... | Rosiglitazone | Metformin | |
| 2 | 19 | 2.03 | 5.97Metformin ==... | Metformin | Insulin | |
| 2 | 18 | 1.93 | 11.84Glipizide ==> ... | Glipizide | Metformin | |
| 2 | 17 | 1.82 | 70.83Metformin & ... | Metformin & Rosiglitazone | Metformin | |
| 2 | 15 | 1.61 | 7.85Insulin ==> M... | Insulin | Metformin | |
| 2 | 15 | 1.61 | 4.72Metformin ==... | Metformin | Rosiglitazone | |
| 3 | 14 | 1.50 | 73.68Metformin ==... | Metformin | Insulin | Insulin |
| 2 | 13 | 1.39 | 6.81Insulin ==> Gl... | Insulin | Glyburide | |
| 2 | 13 | 1.39 | 81.25Metformin & I... | Metformin & Insulin | Insulin | |
| 2 | 13 | 1.39 | 13.54Glyburide ==... | Glyburide | Metformin | |
| 2 | 12 | 1.26 | 3.77Metformin ==... | Metformin | Glyburide | |
| 3 | 12 | 1.26 | 57.14Metformin ==... | Metformin | Glipizide | Glipizide |
| 2 | 11 | 1.18 | 3.46Metformin ==... | Metformin | Glimepiride | |
| 2 | 11 | 1.18 | 11.46Glyburide ==... | Glyburide | Insulin | |
| 2 | 11 | 1.18 | 45.83Metformin & ... | Metformin & Rosiglitazone | Rosiglitazone | |
| 3 | 11 | 1.18 | 6.08Metformin ==... | Metformin | Metformin | Glipizide |
| 3 | 11 | 1.18 | 73.33Insulin ==> M... | Insulin | Metformin | Metformin |
| 2 | 10 | 1.07 | 90.91Insulin & Glyb... | Insulin & Glyburide | Glyburide | |
| 2 | 10 | 1.07 | 90.91Insulin & Glyb... | Insulin & Glyburide | Insulin | |
| 2 | 10 | 1.07 | 55.56Metformin & ... | Metformin & Glipizide | Metformin | |
| 3 | 10 | 1.07 | 55.56Glipizide ==> ... | Glipizide | Metformin | Metformin |

Note that the first few rules do not include switching medications. The first such rule (#17 on the list) is a switch from Metformin to Glipizide followed by a switch from Rosiglitazone to Metformin and Metformin to Insulin. There are some patients with a third item on the chain.

Figure 4. Link Graph for Sequential Market Basket Analysis



Note that the sequential analysis shows fewer connections. Metformin and Insulin remain at the center; Glipizide and Glyburide are now on the spokes. The primary combination drug in use appears to be Metformin and Rosiglitazone. The results are clearer once a time factor is introduced into the model.

RESULTS IN SECOND DATABASE

For the year 2004, there were approximately 350,000 patients in the Diabetes warehouse with approximately 3 million prescriptions for diabetes medications. Because of machine limitations, we used a 50% sample of the database. Medications in this dataset were not identified by name but by class and by NDC codes. NDC codes are different for each drug manufacturer and each dose and configuration of the drug.¹² Therefore, there are many NDC codes for each of the diabetes medications. We use the NDC codes to identify specific medications. Table 4 gives a summary of the prescriptions. We focus on the initial medication for the given year.

Table 4. Number of Prescriptions for First Medication by Patient

| Medication | Number of Prescriptions |
|---------------------|-------------------------|
| Metformin | 63,747 |
| Insulin | 43,941 |
| Glipizide | 10,973 |
| Glyburide | 45,957 |
| Rosiglitazone | 3847 |
| Metformin-Glyburide | 4119 |
| Starlix | 449 |
| Prandin | 977 |
| Precose | 175 |
| Chlorpropamide | 393 |
| Tolbutamide | 62 |
| Tolazamide | 1488 |

Because the database has accurate dates for prescriptions, we can investigate in more detail the occurrence of medication switching using survival data mining. In order to do this, we need to transpose both date and medication. The code for transposing is equal to

```
proc transpose data=medications out=medicationbyid
  prefix=med ;
  id patientid;
run;
```

Doing a similar code to transpose the medication date, we then merge the two transposed datasets together so that both medication and date are in the same observation. We then need to search for the first prescription that involves switching, and the date when the switching occurs. If no switching occurs, we define the final date as a censoring value. The coding used is:

```
data sasuser.survivaldata;
  set medicationbytranspose;
  array meds(379) med_1 - med_379;
  array dates(379) date_1 - date_379;
  do j=1 to 379;
    if dates(j)=. then dates(j)='31dec2004'd;
    censor=1;
  end;
  do i=1 to 379;
    if i=1 then temp=meds(i);
    if meds(i) ne temp then do;
      med_num=i;
      date_num=dates(i);
      medchange=meds(i);
      censor=0;
      i=379;
    end;
  end;
run;
```

The censoring variable can be modified to search for specific endpoint medications. For example, if we want to know whether the change is equal to the drug, Glyburide', then we define glyburide=0 if medchange='glyburide' and =1 otherwise. We also convert the date of switching to a SAS date. The code to do this is added to the data step above:

```
if date_num = . then date_num='12dec2001'd;
if (medchange eq ' ') then censor=1;
if (medchange eq 'Glyburide') then glyburide=0;
else glyburide=1;
if (medchange eq 'Metformin') then metformin=0;
else metformin=1;
if (medchange eq 'Insulin') then insulin=0;
else insulin=1;
finaldate=input(newlastdate, anydtdtm17.);
format finaldate datetime17.;
final=datepart(finaldate);
format final date9.;
```

Then we apply survival analysis stratifying by the initial medication using the start of the year, 2004, as time=0. In doing this, we make the assumption that future medication choice depends on the present medication and not on the past medications. The code is:

```
PROC LIFETEST DATA=sasuser.survival data ALPHA=0.05
;
  BY medchange;
  STRATA med_1;
  TIME Days * censor (1);

RUN;
```

We then change the censor value to other medication values to determine specifically what the patient switched to. Table 5 gives the proportion of medications that were switched by the initial medication at the start of the year. Just

under half the patients (68,000) switched a medication at least once.

Table 5. Failure Rate by Medication

| Medication | Total Prescriptions | Failed | Censored | Percent Censored |
|---------------------|---------------------|--------|----------|------------------|
| Metformin | 63,747 | 13,292 | 50,455 | 79.15 |
| Insulin | 43,941 | 16,621 | 27,320 | 62.17 |
| Glipizide | 10,973 | 7916 | 3057 | 27.86 |
| Glyburide | 45,957 | 29,408 | 16,549 | 36.01 |
| Rosiglitazone | 3847 | 71 | 3776 | 98.15 |
| Metformin-Glyburide | 4119 | 674 | 3445 | 83.64 |
| Starlix | 449 | 0 | 449 | 100.00 |
| Prandin | 977 | 188 | 789 | 80.76 |
| Precose | 175 | 23 | 152 | 86.86 |
| Chlorpropamide | 393 | 191 | 202 | 51.40 |
| Tolbutamide | 62 | 0 | 62 | 100.00 |
| Tolazamide | 1488 | 1 | 1487 | 99.93 |

It is clear that some medications have a higher rate of switching compared to others. In particular, Glipizide and Glyburide in the sulfonylureas class have the highest rate of switching compared to Tolbutamide and Tolazamide in the same class. However, Glipizide and Glyburide are used much more commonly. Metformin has about a 20% switching rate; Metformin and Glyburide combined is only slightly lower at 16%. It is interesting that Insulin has a 38% switching rate, meaning that the patient is moved from insulin to medication, indicating an improvement in the condition of the diabetes, or problems with adverse effects from the insulin.

We next look to see what the patients are switched to. We first look at the medication, Glyburide. A total of 4.76% of the Glipizide patients and 6.62% of the Chlorpropamide patients switch, indicating that Glyburide tends to be a first choice medication and that few patients are switched to it once the patient is taking some other drug. On the other hand, many of the patients are switched to the medication, Metformin (Table 6). Most of the patients who started with Insulin are switched to Metformin (37.83% switched total versus 29.23% switched to Metformin).

Table 6. Switching to Metformin

| Medication | Total Prescriptions | Failed | Censored | Percent Censored |
|---------------------|---------------------|--------|----------|------------------|
| Metformin | 63,747 | 0 | 63,747 | 100.00 |
| Insulin | 43,941 | 13,306 | 30,635 | 69.72 |
| Glipizide | 10,973 | 5454 | 5519 | 50.30 |
| Glyburide | 45,957 | 20,891 | 25,066 | 54.54 |
| Rosiglitazone | 3847 | 0 | 3847 | 100.00 |
| Metformin-Glyburide | 4119 | 0 | 4119 | 100.00 |
| Starlix | 449 | 0 | 449 | 100.00 |
| Prandin | 977 | 0 | 977 | 100.00 |
| Precose | 175 | 0 | 175 | 100.00 |
| Chlorpropamide | 393 | 119 | 274 | 69.72 |
| Tolbutamide | 62 | 0 | 62 | 100.00 |
| Tolazamide | 1488 | 0 | 1488 | 100.00 |

Table 7. Switching to Insulin

| Medication | Total Prescriptions | Failed | Censored | Percent Censored |
|---------------|---------------------|--------|----------|------------------|
| Metformin | 63,747 | 0 | 63,747 | 100.00 |
| Insulin | 43,941 | 0 | 43,941 | 100.00 |
| Glipizide | 10,973 | 1323 | 9650 | 87.94 |
| Glyburide | 45,957 | 5131 | 40,826 | 88.84 |
| Rosiglitazone | 3847 | 0 | 3847 | 100.00 |

| Medication | Total Prescriptions | Failed | Censored | Percent Censored |
|---------------------|---------------------|--------|----------|------------------|
| Metformin-Glyburide | 4119 | 0 | 4119 | 100.00 |
| Starlix | 449 | 0 | 449 | 100.00 |
| Prandin | 977 | 0 | 977 | 100.00 |
| Precose | 175 | 0 | 175 | 100.00 |
| Chlorpropamide | 393 | 12 | 381 | 96.95 |
| Tolbutamide | 62 | 0 | 62 | 100.00 |
| Tolazamide | 1488 | 0 | 1488 | 100.00 |

A switch to Insulin generally indicates progression of the diabetes, and that medications are no longer adequate. Note that this is more likely to occur with the use of Glipizide and Glyburide compared to the other medications.

The median number of prescriptions (issued at 30-day intervals) before the medication is switched is 5 months, with 7 months for a switch to Insulin and 6 for a switch to Metformin. The length of time that elapses between one medication and another indicates that medications are switched rather than added. If added, changes would have an interval of approximately 30 days. This fact is particularly interesting for the drug, Precose, since it is recommended as a second rather than a first medication.

We use the following code to find the third medication used by patients given that they have already used two. We first filter down to only those patients who have a second medication. Then we use the following code:

```

data sasuser.secondsurvival;
  set sasuser.survivaldatafiltered;
  array meds(379) med_1 - med_379;
  array dates(379) date_1 - date_379;
do j=1 to 379;
  if dates(j)=. then dates(j)='31dec2001'd;
end;
do i=med_num to 379;
  if i=med_num then temp2=meds(i);
  if meds(i) ne temp2 then do;
    med_num2=i-med_num-1;
    date_num2=dates(i);
medchange2=meds(i);
    i=379;
  end;
end;
if (medchange2 eq ' ') then censor2=1;
else censor2=0;
if (medchange2 eq 'Glyburide') then glyburide2=0;
else glyburide2=1;
if (medchange2 eq 'Metformin') then metformin2=0;
else metformin2=1;
if (medchange2 eq 'Insulin') then insulin2=0;
else insulin2=1;
newcensor=put(date_num2,mmddyy10.);
finaldate2=input(newcensor,anydtdtm17.);
format finaldate2 datetime17.;

```

The number of patients switching to a third medication is about 17,000. Approximately 72% of those on Glyburide who switch, switch to Metformin, as do 86% of the patients who switch off of Insulin. Of the remaining, 8% of the Glyburide patients and 10% of the Insulin patients who switch move to Rosiglitazone, as do 75% of the patients on Metformin-Glyburide in combination. Of the patients on Rosiglitazone who switch, 97% move to Starlix. The main transition to Insulin is for 17% of the patients on Glyburide who switch. The failure rate by medication is given in Table 8. Note that none of the patients taking Starlix do any switching.

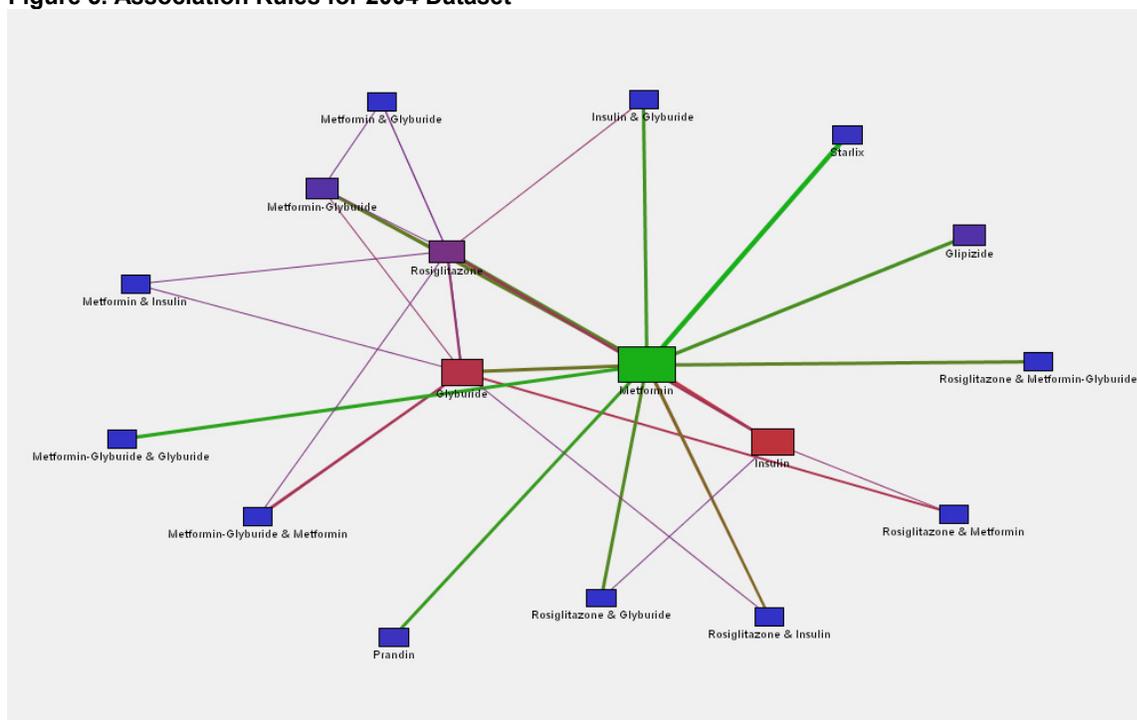
Table 8. Second Medication Switch

| Medication | Total Prescriptions | Failed | Censored | Percent Censored |
|------------|---------------------|--------|----------|------------------|
| Metformin | 39,772 | 9637 | 30,135 | 75.77 |

| Medication | Total Prescriptions | Failed | Censored | Percent Censored |
|---------------------|---------------------|--------|----------|------------------|
| Insulin | 6468 | 4631 | 1837 | 28.40 |
| Glipizide | 9 | 6 | 3 | 33.33 |
| Glyburide | 548 | 427 | 121 | 22.08 |
| Rosiglitazone | 11,826 | 294 | 11,532 | 97.51 |
| Metformin-Glyburide | 5499 | 1173 | 4326 | 78.67 |
| Starlix | 982 | 0 | 982 | 100.00 |
| Prandin | 1806 | 489 | 1317 | 72.92 |
| Precose | 531 | 155 | 376 | 70.81 |
| Tolbutamide | 51 | 0 | 51 | 100.00 |
| Tolazamide | 897 | 1 | 896 | 99.89 |

The second switch in medications occurred at a median of 3 months, down from 5 months for the first switch. Figure 5 gives the association rules for this dataset.

Figure 5. Association Rules for 2004 Dataset



Note that there are two central points, Glyburide and Metformin, with Metformin as the larger center. It indicates that Glyburide remains a starting point, contrary to the Guidelines in Figure 2.

USE OF A1C TESTING

The guidelines in Figures 1 and 2 suggest that medications should be added depending upon the value of the A1C test rather than switched. Therefore, we want to go to the labs dataset to look at the labs ordered to see if the switch in medications occurs in relationship to testing. The claims will not have test results; only the fact that the test was ordered.

To examine the use of A1C testing, we look at the outpatient data file. A1C is identified by the CPT code, 83036. We filter the dataset using this code. Since there are multiple A1C tests per patient, we again use PROC Transpose on the test dates and then merge the resulting dataset with the dataset of medications.

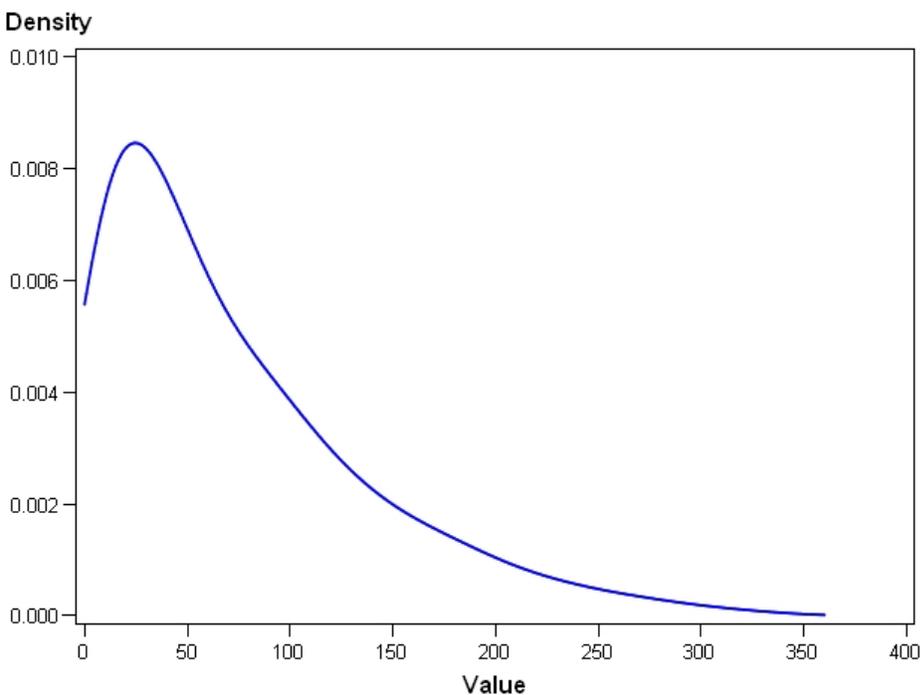
Of the 170,000 patients taking diabetes medications in our sample, only 42,000 have any A1C test. That number drops to 14,000 for a second test in the year. The A1C should be tested at 3-month intervals, meaning that each patient should have 4-5 tests in the year. In contrast, 670 patients have 7 or more A1C tests and 67 have over a dozen A1C tests in 2004.

To examine the relationship between A1C and switching medications, we use the code:

```
data Sasuser.A1Cmeds;
set sasuser.Merged;
x1=datdif(final,A1Cdate_1,'ACT/ACT');
if (A1Cdate_2 ne '.') then x2=datdif(final,A1Cdate_2);
else x1=x2;
if (A1Cdate_3 ne '.') then x3=datdif(final,A1Cdate_3);
else x3=x2;
diff = min(abs(x1),abs(x2),abs(x3));
```

In this way, we look at the minimum elapsed time between the A1C and switching medications. The average (median) difference between switching medications and the A1C test is 72 days (53 days). The kernel density estimation (PROC KDE) is given in Figure 6. It indicates that the peak of the distribution occurs at 50 days with a heavy tail up to 350 days. Therefore, there is mostly a 50-day difference between the A1C test and a new prescription, when an A1C is used at all.

Figure 6. Kernel Density Estimation



The question is whether this elapsed time is reasonable; that is whether there is a timely response to the results of the A1C test. We compare the time to switching medications first by using kernel density estimation (Figure 7) and then by using survival analysis (Figure 8) for patients with and without an A1C test.

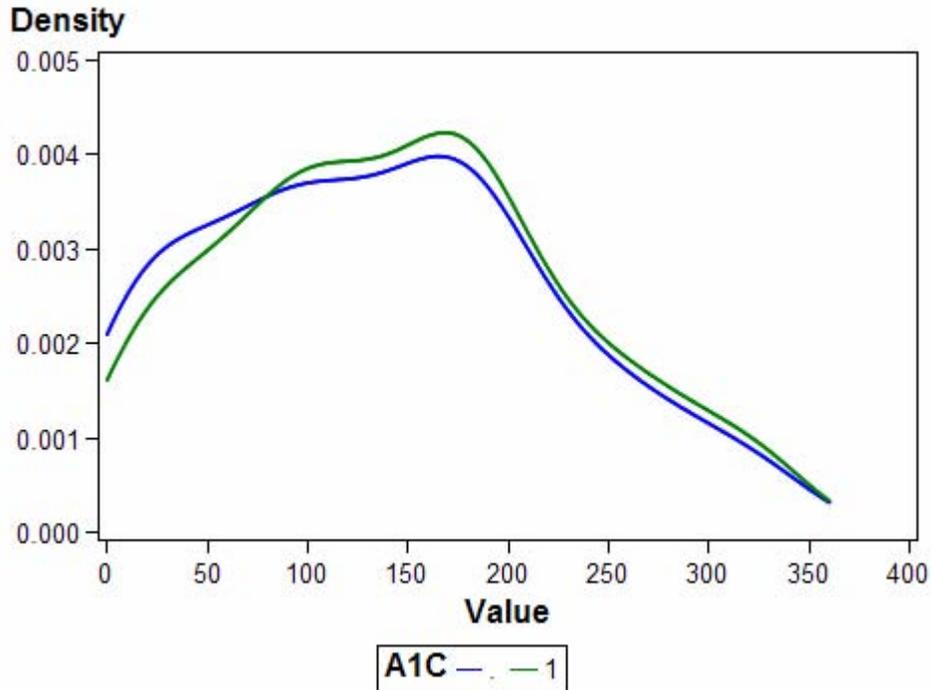
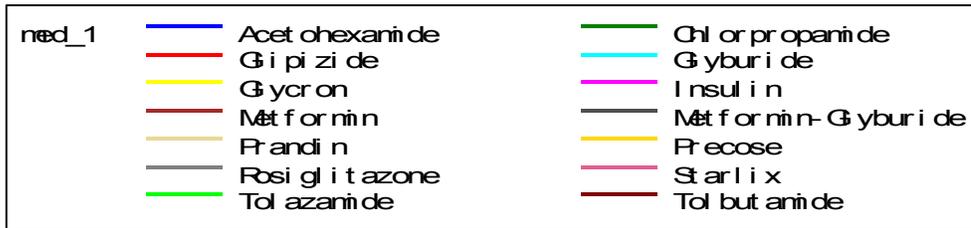
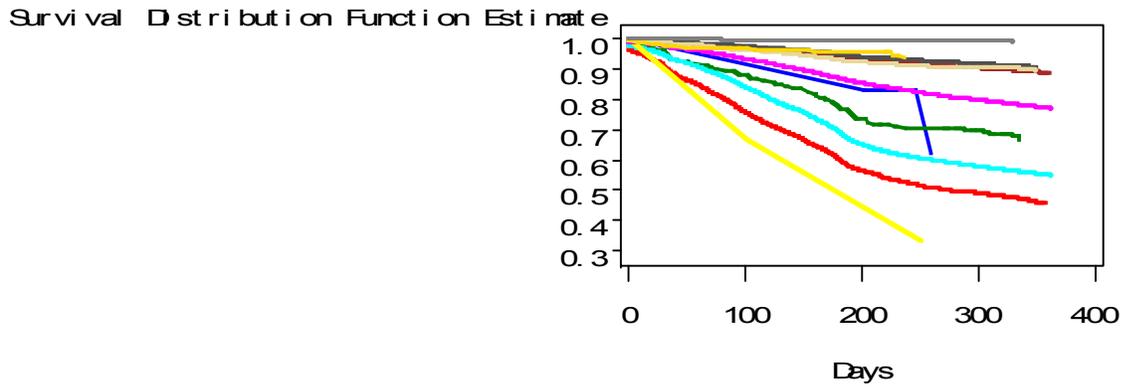
Figure 7. Comparison of Switching for Patients With A1C and Without A1C

Figure 7 indicates that there is no real difference in the likelihood of switching with and without the use of the A1C test. The probability density curves are virtually identical. It is possible that physicians are using the recommendations given in Figure 1 and using fasting glucose levels rather than the A1C. Further study will include use of 2007 data to see if more physicians are using the A1C recommendations.

Figure 8. Survival Analysis for Switching Medications With and Without A1C
 A. Without A1C

Line Plot

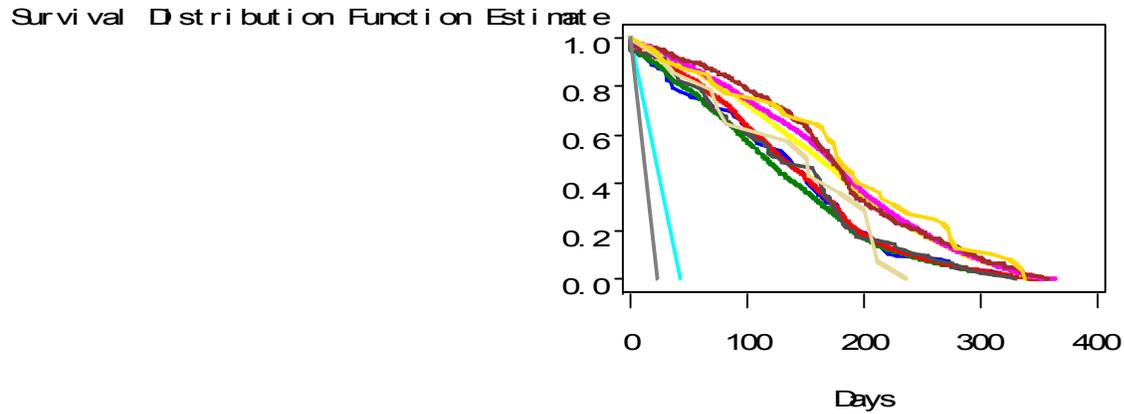
A1C_Test = 0



B. With A1C

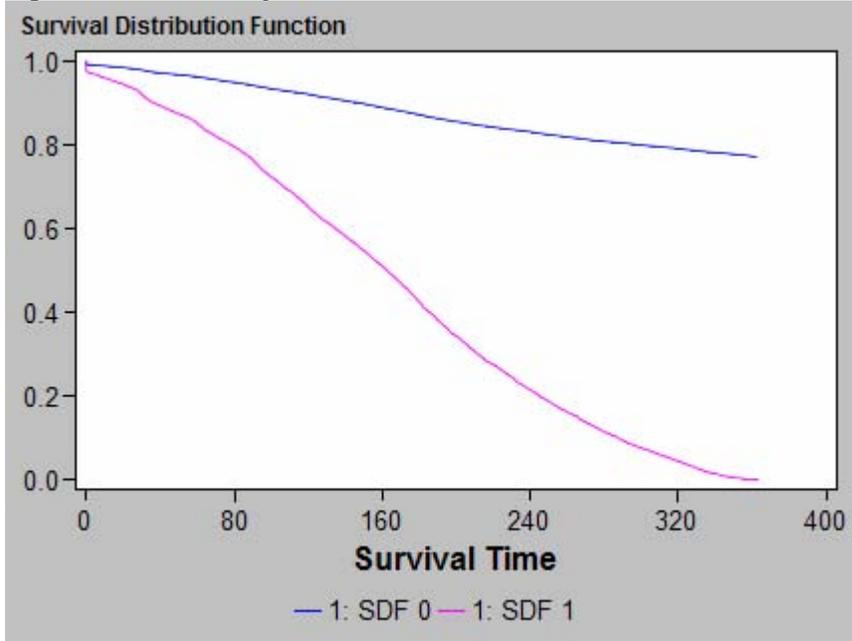
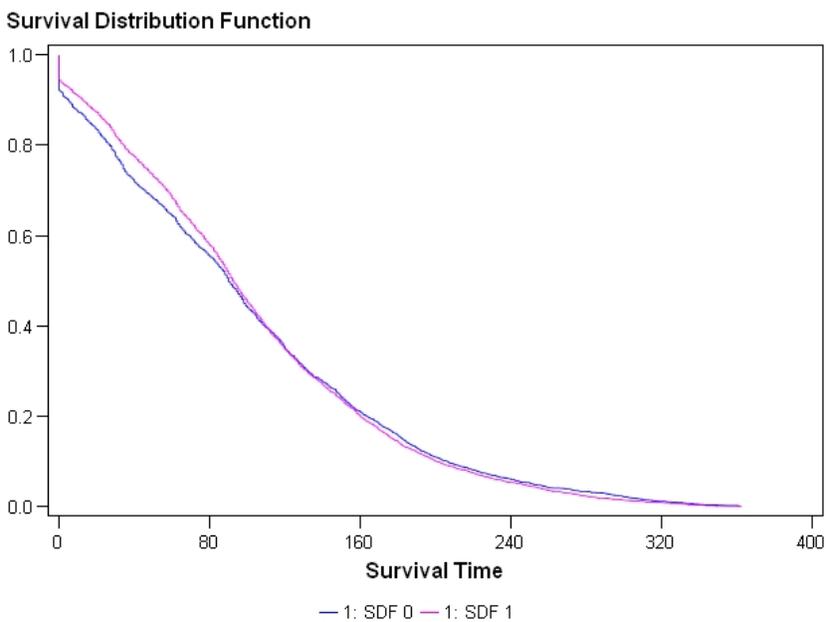
Line Plot

A1C_Test =1



Patients without the A1C are much less likely to switch to a new medication compared to those patients with at least one A1C. However, regardless of the base medication, use of the A1C test is not universal.

Because a switch from Insulin to medication and conversely represents a critical progression of the disease, we filter down to where Insulin is the first drug and switched, and then filter to where Insulin is the switched drug. We want to determine whether this switch is specifically accompanied by an A1C test. Unfortunately, as shown in Figure 9, the A1C is not used universally when Insulin is prescribed. It does show that the patient is less likely to be switched from Insulin without an A1C compared to switching with an A1C. In Figure 10, it shows that a switch to Insulin is equally likely with or without an A1C.

Figure 9. Survival Analysis With and Without A1C for Insulin to Medication**Figure 10. Survival Analysis With and Without A1C for Medication to Insulin****CONCLUSION**

When there are many medications available to treat one patient condition, we need to investigate just how the drugs

are prescribed by physician. Switching or adding medications suggests that the initial treatment is not effective, or has ceased to be effective. We can examine switching to find patterns of effectiveness or ineffectiveness.

Data mining combinations of treatments and tests are important to investigate connections between combinations of decisions. Survival data mining, kernel density estimation, and market basket analysis enable us to examine combinations of treatments. Preprocessing of data is crucial in using these techniques.

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