USE OF NATIONAL ELECTRONIC HEALTH RECORD (EHR) DATA WAREHOUSE TO IDENTIFY INAPPROPRIATE HBA1C ORDERS FOR SICKLE CELL DISEASE PATIENTS

A THESIS IN
Bioinformatics

Presented to the Faculty of the University
of Missouri-Kansas City in partial fulfillment of
the requirements of the degree

MASTER OF SCIENCE

by
SHIVANI SIVASANKAR

B.Tech., Jeppiaar Engineering College, Affiliated to Anna University, 2016

Kansas City, Missouri

2018

USE OF NATIONAL ELECTRONIC HEALTH RECORD (EHR) DATA WAREHOUSE TO IDENTIFY INAPPROPRIATE HBA1C ORDERS FOR SICKLE CELL DISEASE PATIENTS

Shivani Sivasankar, Candidate for the Master of Science Degree

University of Missouri-Kansas City, 2018

ABSTRACT

The glycated Hemoglobin (HbA1c) test is one of the most important diagnostic and prognostic strategies for monitoring diabetes. However, the clinical utility of this test is questionable for sickle cell disease patients, who are homozygous for a variant hemoglobin gene (HBB). While there have been analyses from individual provider organizations, no prior national level analysis of the HbA1c ordering practice for sickle cell disease patients has been performed. A national level assessment could serve as a baseline to evaluate this quality concern in individual health care settings. The main objective of this study was to evaluate the frequency of the inappropriate HbA1c test orders and the prevalence of the more appropriate fructosamine test orders as an alternative to HbA1c test, nationally and at Truman Medical Center (TMC) in Kansas City, MO. We analyzed de-identified, HIPAA compliant, electronic health record (EHR) data in the Cerner Health Facts ™ (HF) data warehouse. We identified the frequency of inappropriate orders of HbA1c tests by comparing the 526 Sickle cell patients in TMC with 36,625 sickle cell patients from 393 national facilities in the data warehouse. The

linear unbiased percentages estimated from the Generalized Linear Mixed Model (GLMM) was used to rank the TMC with other national hospitals based on the percentage of sickle cell patients with inappropriate HbA1c test. TMC had a significantly higher percentage of sickle cell patients with HbA1c tests when compared to the national hospital cohort (32% versus 11%). The results showed that TMC ranks in the bottom 25% quartile of the 393 qualifying facilities with respect to inappropriate HbA1c orders. Interestingly, TMC sickle cell patients were ten-fold more likely to have at least one fructosamine encounter when compared to the sickle cell patients in the other 10 national hospitals which had fructosamine encounters (11% versus 1%). However, there was still a significantly higher number of sickle cell disease patients in TMC than in other national hospitals who had only HbA1c tests (24% versus 10%). These findings indicate that inappropriate HbA1c orders in sickle cell patients is a potential quality concern at TMC which can be addressed with sustainable interventions so that overtreatment or under-treatment of the diabetic condition in sickle cell patients are avoided.

APPROVAL PAGE

The faculty listed below, appointed by the Dean of the School of Medicine have examined a thesis titled "Use of National Electronic Health Record (EHR) Data Warehouse to Identify Inappropriate HbA1c Orders for Sickle cell Disease Patients", presented by Shivani Sivasankar, candidate for the Master of Science degree, and certify that in their opinion it is worthy of acceptance.

Supervisory Committee

An-Lin Cheng, Ph.D., Committee Chair
Department of Biomedical and Health Informatics

Mark Hoffman, Ph.D.
Department of Biomedical and Health Informatics

Kamani Lankachandra, MD, FCAP.
Department of Pathology

CONTENTS

ILLUSTRATIONS

Figures Pages

TABLES

Table Pages

ACKNOWLEDGEMENTS

I am grateful to Dr.An-Lin Cheng for her instructions, guidance, progress monitoring, and support. She had to bear lot of patience in training me on data analysis using Statistical Analysis Software. I would also like to extend my gratitude to Dr.Mark Hoffman for his knowledge, encouragement, and invaluable support with patience. He was always very helpful whenever I ran into a trouble spot or had a question about my research or writing. Thank you for shining a bright light on the magnitude of bioinformatics and Electronic Health Records. I would also like to express my gratitude to Dr.Kamani Lankachandra for the encouragement, guidance and supervision. Without her passionate participation and input, this research could not have been successfully conducted. I'm also thankful to Suman Sahil for making sure I understood the complexities involved in analyzing the HealthFacts dataset. I would also like to extend my gratitude to the rest of the project team, Robyn Johnson, Jeremy Provance, Shaun Ferguson and Allison Epps who played an important role in the successful completion of the project. My last, but certainly not least, acknowledgement goes to my family and friends for supporting me through this process. I wouldn't be where I am without the love, help, and encouragement from you all. Thank you.

CHAPTER 1

INTRODUCTION

Sickle cell disease (SCD) is one of the most common severe monogenic hematological disorders worldwide. It is a multi-system disease that leads to the abnormal structure of the globin chains of the hemoglobin molecule depending on the exact mutation in each hemoglobin gene (Kohne, 2011; Weatherall & Clegg, 2001). In United States, the sickle gene is present in approximately 8% of the African-American population. SCD is estimated to affect 100,000 Americans where it occurs among 1 out of every 365 African-American births and among 1 out of every 16,300 Hispanic-American births (CDC, 2016). The glycated hemoglobin A1c (HbA1c) test measures glucose bound to hemoglobin and is used to monitor long term glycemic control and for diagnosing diabetes mellitus (Lenters-Westra, Schindhelm, Bilo, & Slingerland, 2013). However, the clinical utility of this test is questionable for Sickle cell disease patients. Of the estimated 366 million individuals with diabetes mellitus in 2011, around 26 million also had a hemoglobin (Hb) disorder (Whiting, Guariguata, Weil, & Shaw, 2011). In this study we focus on patients who are homozygous for a variant gene (HbS, HbC, HbE, Hb-G, Hb-J, Hb-K, Hb-O, Hb-P)(Rees, Williams, & Gladwin, 2010a). In these patients, the glycated form of the hemoglobin variant polymerize together leading to erythrocyte rigidity and vaso- occlusion. Therefore, these erythrocytes have a shorter lifespan (10-20 days) compared to a normal erythrocyte (90-120 days)(Kohne, 2011). The presence of hemoglobin variants, could affect the net charge of the hemoglobin and the recognition of the glycated N terminus by antibodies thereby resulting in erroneous HbA1c values. The

hemoglobin variants affect the HbA1c test as it alters the normal process of glycation of HbA to A1C which produces an abnormal peak on chromatography, making estimation of HbA1C unreliable. As the measurement of HbA1c is dependent on normal erythrocyte life span, conditions like abnormal red cell turnover, anemia and blood transfusions may also interfere with the validity of HbA1c measurement as it decreases the time for glycosylation to occur thereby producing a falsely low A1C result (Lippi & Targher, 2011; Speeckaert et al., 2014). Therefore, the accuracy of the HbA1c measurement, can be adversely affected due to the qualitative and quantitative differences in hemoglobin by the presence of these hemoglobin variants.

Hemoglobin variants can affect HbA1c levels leading to the use of alternative measures for glycemic control that are not based on hemoglobin among these patients (Bry, Chen, & Sacks, 2001; Gunton & McElduff, 2000; Schnedl et al., 2000; Smaldone, 2008; Tran, Silva, & Petrovsky, 2004). The alternative measure of glycemic index primarily includes the fructosamine test, glycated albumin test and 1,5,anhydroglucitol. However, the latter two tests are not as extensively evaluated in clinical settings as fructosamine (Speeckaert et al., 2014). The total concentration of fructosamine is predominantly a measure of glycated albumin and a minor contribution of other circulatory proteins such as glycated lipoproteins and glycated globulins (Cohen, Holmes, Chenier, & Joiner, 2003). Several studies have established cut-offs and correlations to glucose and HbA1c confirming that fructosamine test is a useful indicator of hyperglycemia (Baker, Metcalf, Holdaway, & Johnson, 1985; Baker, Metcalf, Johnson, Newman, & Rietz, 1985; Baker, O'Connor, Metcalf, Lawson, & Johnson, 1983; Cohen et

al., 2003; Juraschek, Steffes, & Selvin, 2012; Ko et al., 1998; Malmström et al., 2014; Selvin et al., 2014). Accordingly, the measurement of fructosamine either as a standalone indicator of hyperglycemia or in combination with glucose and HbA1c would potentially be a useful tool in conditions in which HbA1c is unreliable.

As such, inappropriate use of HbA1c as a standalone test for Sickle cell disease patients to diagnose or screen diabetes is a major quality concern in health care as it might lead to overtreatment or under-treatment of the diabetic condition in these patients. Sustainable interventions such as the assessment of other indices of chronic glycemia are recommended for these patients (Juraschek et al., 2012). While there have been analyses from individual provider organizations (Atabani et al., 1989; Reid et al., 1992; Weykamp et al., 1993; Lacy et al., 2017), no prior national level assessment of this ordering practice has been performed. This national level assessment could serve as a baseline to evaluate this quality concern in individual health care settings.

Electronic Health Records (EHR) are a comprehensive, cross-institutional and longitudinal collection of patient's health care data (Hoerbst & Ammenwerth, 2010). Several studies have demonstrated that EHR systems promote cost-effective and sustainable solutions for improving quality in medical care (Hillestad et al., 2005; Johnston, Langton, Haynes, & Mathieu, 1994; Wang et al., 2003). Access to data derived from the EHR in multi-institutional data warehouses provide a powerful resource for national level assessment, to compare practices and outcomes across independent, non-affiliated, organizations to guide and identify quality improvement initiatives. Any public health challenge concern requires joint effort from academic researchers in collaboration

with clinical and public health practitioners, to identify quality gaps and to implement sustainable interventions (Ammerman, Smith, & Calancie, 2014). This approach, known as Practice Based Evidence (PBE), is an integral aspect of the Institute of Medicine (IOM) Learning Healthcare System strategy and can be performed by analyzing data generated during the delivery of the patient care (Smith, Halvorson, & Kaplan, 2012). This approach is different from the Evidence-based medicine (EBM) approach which requires systematic review of the published literature, engagement of experts on the topic and abstraction and reconciliation of knowledge from disparate sources. The PBE approach overcomes the challenges of EBM which include frequent gaps in the literature (including the literature related to laboratory quality improvement), limited resources to support the engagement of a panel of experts and the lengthy time required to complete a comprehensive EBM analysis. Often quality improvement (QI) projects are selected in reaction to a recent adverse event. While this is frequently necessary after a critical issue, it may also result in failure to recognize deeper systemic quality gaps in which an organization is at significant variance from their peers. With respect to laboratory quality improvement, there is a significant opportunity to apply the PBE strategy to the recognition of quality gaps, the selection of critical quality improvement projects and comparison with facilities with a high and low frequencies of the quality gap in order to inform interventions (Green, 2008).

This study utilized a Practice Based Evidence approach by analyzing a de-identified, HIPAA compliant, electronic health record (EHR) data in the Cerner Health Facts ™ (HF) national data warehouse. Truman Medical Centers (TMC), Kansas City,

MO, is a contributor to this national data warehouse. This was implemented by quantifying the frequency of Sickle cell patients with inappropriate HbA1c orders and the prevalence of fructosamine orders in TMC and by comparing this ordering practice across other independent, non-affiliated organizations in the national data warehouse. The present analysis of this large clinical national data warehouse was undertaken to guide TMC in identifying and evaluating this potential quality concern.

CHAPTER 2

REVIEW OF LITERATURE

Sickle cell Disease

Sickle cell disease (SCD) is a collection of blood-disorders which occurs when a person inherits two abnormal copies of the hemoglobin gene, one from each parent (Rees, Williams, & Gladwin, 2010b). There are more than 1300 known hemoglobin variants, with the majority of them rare in prevalence while some reach high frequencies in specific population groups (Patrinos, G.P., B. Giardine, C. Riemer, W. Miller, D.H.K. Chui, N.P. Anagnou, H. Wajcman, and R.C. Hardison, 2004). The most common type is the Sickle cell anemia (homozygous HbSS) which results due to the inheritance of Glu6Val mutation in the HBB gene from both parents and permits the formation of the pathological sickle hemoglobin tetramer(Ware, Montalembert, Tshilolo, & Abboud, 2017). This abnormal mutant hemoglobin S, undergoes intracellular polymerization and feature the propensity of erythrocytes to stick together and form long molecules by stretching the normal flexible biconcave shape into sickle shape cells on deoxygenation. These sickle-shaped cells are rigid and can die prematurely, blocking small blood vessels and causing vaso-occlusion. This can lead to anemia, severe pain, infection, infarction, acute illness and progressive chronic organ complications, including cardiopulmonary, renal and vascular dysfunction (Elmariah et al., 2014; Powars, Chan, Hiti, Ramicone, & Johnson, 2005). The diagnosis of Sickle cell disease is relatively simple, using techniques such as electrophoresis which separate normal from variant hemoglobin using standard

alkaline gel, isoelectric focusing, capillary electrophoresis or high performance liquid chromatography (Ware et al., 2017).

According to a published estimate, in 2010 there were 312,302 newborns born with Sickle cell anemia and over half of them were born in Africa, India, Eastern Mediterranean and Middle East (Piel et al., 2013). The 2015 Global Burden of Disease report includes Sickle cell disease as causing more than 100,000 deaths which represents a 6% increase in prevalence since 2005 (Global Burden of Disease Study 2013 Collaborators, 2015). Individuals with Sickle cell trait, (heterozygous HbAS) have some resistance to the often fatal malaria, a likely explanation for the persistence and the distribution of the sickle gene in the malaria-endemic tropic and sub-tropic areas (Piel et al., 2010). Even though Sickle cell disease were originally characteristic of the tropics and the sub-tropics, they are now encountered world-wide due to migrations of population (Weatherall & Clegg, 2001).

Hemoglobin A1c Test

Diabetes mellitus is a frequent disorder affecting individuals of all ages. Glycohemoglobin has a key role in the assessment of glycemic control in diabetic patients. Glycated hemoglobin is hemoglobin that has been irreversibly modified by addition of a glucose through a non-enzymatic process and provides a weighted average of plasma glucose concentration over the erythrocyte lifespan (Camargo & Gross, 2004). It has a key role in the assessment of glycemic control which is strongly associated with development and progression of diabetic complications in both type 1 and 2 diabetes mellitus. In the presence of excess plasma glucose, the hemoglobin beta-chain becomes

increasingly glycosylated, making the A1C a useful index of glycemic control in patients with diabetes mellitus (Kawano, 1999). Normally in most individuals, Hb consists of ~97% HbA, <2.5% HbA2 and 0.5% HbF (Sacks, 2012). In healthy individuals, 6% of the HbA is glycated to form HbA1a, HbA1b and HbA1c (Lenters-Westra et al., 2013). HbA1c results from the attachment of a glucose molecule to the N-terminal valine of the Hb β-globin chain and the rate of HbA1c production is directly proportional to the ambient glucose concentration (Bry et al., 2001). This has been expressed as a ratio (HbA1c/total Hb) in order to compensate for intra- and interindividual variation in the total Hb concentration (C. Weykamp, John, & Mosca, 2009). The long life-span of erythrocytes (On average, 117 days in men and 106 days in women) enable the measurement of HbA1c to be used as an index of glycemic control over the preceding two to three months and correlate well with the risk for the development of chronic complications related to diabetes (Jeffcoate, 2004). The current diagnostic criteria for the diagnosis of diabetes as published by the American Diabetes Association (ADA) is based on the HbA1c value >6.5% (ie, > 48 mmol/mol), while an increased risk of diabetes (ie, prediabetes) is based on the HbA1c value 5.7 - 6.4% (ie, 39–46 mmol/mol) (American Diabetes Association, 2014).

The HbA1c test is not foolproof and some of the well-recognized drawbacks include lower diagnostic efficiency in specific populations (pregnant women, elderly and non-Hispanic blacks) or end-stage renal disease or heavy alcohol consumption; risk of over-diagnosing diabetes in presence of iron deficiency anemia or Vitamin B12 deficiency or rheumatoid arthritis or in cases of certain hemoglobinopathies (El-Agouza,

Abu Shahla, & Sirdah, 2002; Jiao, Okumiya, Saibara, Park, & Sasaki, 1998; Lippi & Targher, 2010; Uzu et al., 2009). One of the major factors that affect the accuracy of HbA1c measurements depends on the assay method and the specific hemoglobin variant. There are two forms of glycated Hb in heterozygous individuals carrying HbA and the variant Hb gene (HbAS, HbAE, HbAC etc). This may result in the deviation of HbA1c which may lead to over- or under-treatment of diabetic patients (Lacy et al., 2017). Extensive work has been done by the NGSP (National Glycohemoglobin Standardization Program) to standardize the appropriate methods that can be used to measure HbA1c even in the presence of hemoglobin variants (NGSP: Factors that Interfere with HbA1c Test Results, 2014.). ADA has acknowledged that in patients with Sickle cell disease, for whom HbA1c is unreliable due to the altered red cell turnover, the assessment of other indices of chronic glycemia may be advisable. These alternative measures include fructosamine and glycated albumin (GA).

Fructosamine Test

Fructosamine (1-amino-1-deoxy-D-fructose) represents a clinically accessible measure of non-enzymatic glycation of proteins in the same compartment as plasma glucose and should integrate plasma glucose fluctuations. The total concentration of fructosamine is a measure of glycated albumin, along with the contribution of other circulatory proteins such as glycated lipoproteins and glycated globulins (Cohen et al., 2003). It is a simple, robust and inexpensive biomarker that gives an earlier indication of poorly controlled glucose compared to HbA1c for diabetic patients (True, 2009). However, as the half-life of non-immunoglobin serum proteins is much lower (~14-21

days) compared to red blood cells (~90 to 120 days), this means that fructosamine provides a short term glycemic control (previous two weeks) compared to HbA1c test which provides a long term glycemic control (over a period of 2-3 months)(Roohk & Zaidi, 2008). Another important difference is that the rate of non-enzymatic glycation of the proteins are 9-10 fold higher than hemoglobin. As a consequence, the blood levels of fructosamine exhibit a broader fluctuation than those of HbA1c (Rondeau & Bourdon, 2011).

Electronic Health Records

Electronic Health records (EHR) have been shown to coordinate care, routinely measure quality or reduce medical errors. This can facilitate workflow and improve the quality of patient care which can provide substantial benefits to physicians, clinics and health care organizations (Elson & Connelly, 1995). The implementation of the "meaningful use" criteria for EHR, mandated by the Health Information Technology for Economic and Clinical Health (HITECH) Act of 2009 has committed unprecedented resources to supporting the adoption and use of EHRs. The HITECH legislation further required that meaningful use include electronic reporting of data on the quality of care. This funding will provide important support to achieve liftoff for the creation of a nationwide system of EHRs (Blumenthal & Tavenner, 2010). However, analyses of electronic health record (EHR) data, is challenging as it contains valuable yet heterogenous and complex data in terms of missing values, inconsistent records and high dimensionality (Miller & Sim, 2004). As it is not possible to control the circumstances under which the measurements are taken in the EHR, there may be considerable variation

in the observations due to the differences in practice, policy and personnel in different facilities. The data is uncorrelated as it is drawn from a hierarchy of different populations These observations also exhibit dependency as measurements of different attributes are taken from the same patient over time.

In this study we have used a multi-institutional national data warehouse to identify and quantify a potential quality concern in the Truman Medical Centers (TMC) by comparing the mis-utilization of HbA1c orders in Sickle cell disease patients with other national hospitals. TMC are the primary safety net facilities for Jackson County MO area which consist of two hospitals totaling 600 beds, outpatient clinics and a behavioral health center. The Hospital Hill campus of TMC serves the urban core of Kansas City, Missouri and provides 249 acute, 52 Emergency Department bed hospital, a Level One trauma center, a Level Three NICU and a dedicated Sickle cell disease center. The Lakewood campus serves the eastern suburbs of Jackson, County Missouri.

The main objective of the present study was to evaluate the inappropriate HbA1c test orders for Sickle cell patients as a major quality concern by implementing the practice based evidence model using the national data warehouse, Health Facts database (Cerner Corporation, Kansas City, MO). This study also ranks TMC with other national hospitals in terms of its percentage of Sickle cell patients by implementing the Generalized Linear Mixed Model. An additional objective was to evaluate the utilization of the fructosamine test for Sickle cell patients relative to the HbA1c test in TMC compared to other national hospitals.

CHAPTER 3

METHODOLOGY

Data Source

This study uses the Health Facts database (Cerner Corporation, Kansas City, MO), a national data warehouse that collects comprehensive clinical records across healthcare facilities throughout the United States. Health Facts is a voluntary program offered to organizations using the Cerner Electronic Health Record (EHR). The database contains data systematically extracted from participating institution's EHR and includes encounter data (emergency, outpatient, and inpatient), patient demographics (age, sex, and race), diagnoses and in-hospital procedures documented by ICD-9-CM and ICD-10-CM codes, laboratory data documented by LOINC codes and facility characteristics (census region, number of beds, acute setting and teaching versus nonteaching status). This comprises of about 5.1 billion encounters (clinical care events) from 64 million patients in 863 healthcare facilities. All admissions, medication orders and dispensing, laboratory orders and specimens are date and time stamped, providing a temporal relationship between treatment patterns and clinical information. All data were deidentified in compliance with the Health Insurance Portability and Accountability Act (HIPAA) of 1996 before being provided to the investigators. Longitudinal connection between patient encounters within the same health system is preserved (Strack et al., 2014).

.

Study Cohort

We conducted a retrospective analysis of patients admitted to the hospital with Sickle cell disease between January 2010 and December 2016. Of the 863 facilities in Health Facts, 393 had a qualifying Sickle cell population. We included all patients with a diagnosis of Sickle cell disease using International Classification of Diseases, Ninth Revision and Tenth Revision, Clinical Modification codes (ICD-9-CM and ICD-10-CM). The codes were selected based on clinical judgement and in combination with an existing published study to identify Sickle cell disease cohort within electronic health records using ICD-9-CM diagnosis codes (Michalik, Taylor, & Panepinto, 2017). The phenotypes were further validated using PheKB resource. The Phenotype Knowledgebase website (PheKB) is a collaborative environment to build and validate electronic algorithms that can identify characteristics of patients within health data. It has tools that can view existing algorithms, create and validate new algorithms, collaborate with others to create or review algorithms and view implementation details for existing algorithms (Kirby et al., 2016). The resulting definition groups (from ICD-9-CM codes) were combined with the appropriate ICD-10-CM codes to identify the Sickle cell disease patient cohort (Table 1). This data represents integrated delivery networks throughout the United States: Midwest (79 hospitals), Northeast (68 hospitals), South (162 hospitals), and West (84 hospitals). Most of the hospitals (239 hospitals) have bed size less than 100, 133 hospitals have bed size between 100 to 500 and bed size of 21 hospitals is greater than 500.

Table 1. The ICD-9 and ICD-10 CM codes used in this study to identify the Sickle cell population which are grouped together based on consensus definition from PheKB resource

Definition	**ICD -9 CM Codes**	**ICD-10 CM Codes**
Sickle cell thalassemia without crisis	282.41	D57.4 D57.40
Sickle cell thalassemia with crisis	282.42	D57.41 D57.411 D57.412 D57.419
HbSS disease unspecified	282.6 282.60	D57
HbSS disease without crisis	282.61	D57.1
HbSS disease with crisis	282.62	D57.0 D57.01 D57.02
Sickle cell/HbC disease without crisis	282.63	D57.20
Sickle cell/HbC disease with crisis	282.64	D57.2 D57.21 D57.211 D57.212 D57.219
Other Sickle cell disease without crisis (Hb-D) (Hb-E) (Hb-G) (Hb-J) (Hb-K) (Hb-O) (Hb-P)	282.68	D57.8 D57.80
Other Sickle cell disease with crisis (Hb-D) (Hb-E) (Hb-G) (Hb-J) (Hb-K) (Hb-O) (Hb-P)	282.69	D57.81 D57.811 D57.812 D57.819

The majority of the hospitals (300 hospitals) are urban while 93 hospitals are rural. As this data represents integrated delivery network health systems in addition to stand-alone hospitals, the data contains both inpatient and outpatient data, including emergency department, for the same group of patients.

Extraction of Initial Data from the Database

The data was initially extracted from the Health Facts database for all encounters that had a diagnosis of Sickle cell disease (using the ICD-9-CM and ICD-10-CM codes) between 2010 and 2016. This Sickle cell-patient cohort was further analyzed for HbA1c encounters based on the criteria that it included all patients with a HbA1c test order (identified by LOINC codes: 55454-3, 41995-2, 4548-4, 17855-8, 4549-2, 17856-6) after the diagnosis of Sickle cell disease. The Sickle cell patient cohort was also analyzed for fructosamine encounters based on the criteria that it included all patients with a fructosamine test (identified by LOINC codes: 33805-3, 15069-8, 53550-0) after the diagnosis of Sickle cell disease. HbA1c and Fructosamine encounters before 2010 and after 2016 were excluded from the analysis in order to avoid data partial in nature.

Analysis

The unit of our analysis are the sickle cell patients with at least one HbA1c or Fructosamine encounter after the presence of a sickle cell diagnosis. For example, a sickle cell patient will be tagged with HbA1c in a year, if the patient had at least one HbA1c encounter in that particular year. The baseline demographic characteristics and sickle cell diagnosis groups were compared between the sickle cell patients in TMC and other national hospitals. Based on the patient population from the sickle cell-A1c dataset,

we considered two groups of encounters: (i) no HbA1c test ordered for a sickle cell patient after sickle cell diagnosis in TMC compared to all the facilities, (ii) HbA1c test ordered for a sickle cell patient after sickle cell diagnosis in TMC compared to all the facilities. The latter group represents potentially inappropriate ordering of HbA1c test.

Based on the patient population from the sickle cell-fructosamine dataset, we considered two groups of encounters: (i) no Fructosamine test ordered for a sickle cell patient after sickle cell diagnosis in TMC compared to all the facilities, (ii) Fructosamine test ordered for a sickle cell patient after sickle cell diagnosis in TMC compared to all the facilities. These fructosamine encounters were further analyzed in relation to A1c encounters in TMC compared to other national hospitals where we considered the following three groups (i) Sickle cell patients with only A1c encounters (ii) Sickle cell patients with only fructosamine encounters and (iii) Sickle cell patients with both HbA1c and Fructosmine encounters. The latter group was further analyzed to evaluate the ordering pattern of A1c orders relative to Fructosamine in TMC compared to other national hospitals.

In order to identify if TMC is ranked lower compared to the other national hospitals for the inappropriate orders of HbA1c tests for sickle cell patients and to account for the random effects inherent within this diverse dataset and the bias from possible covariates, the Generalized Linear Mixed Model (GLMM) was implemented to estimate the best linear unbiased predictors as percent ordered for every hospital at each year. A generalized linear mixed model is a statistical model that extends the class of

generalized linear models by incorporating normally distributed random effects (Schabenberger, 2005).

The percent of sickle cell patients with HbA1c test orders was taken as the outcome variable. Hospital level demographic information such as, census region classification, teaching facility or not, urban/ rural location, acute setting and bed size were included in the model to account for possible bias. The number of sickle patients were also included in the model to account for the different number of sickle patients observed at each facility. The PROC GLIMMIX procedure in SAS was used with link function equals to logit for proportion outcome (Schabenberger, 2005). Using this model, hospital-specific linear unbiased percentage were generated. This represents the percentage of sickle cell disease patients with HbA1c orders in each hospital at each year. The estimated percentages for every hospital were ranked to identify the distribution of TMC in a quartile. The analysis was performed in SAS statistical software. Graphics from R language was used to interpret the ranking of the percentages into quartiles.

Ethical and Legal Issues

This research is based on a pre-existing HIPAA compliant dataset that contains no personally identifiable information. The UMKC Institutional Review Board has determined that all work with Health Facts is considered “non human subjects” research.

CHAPTER 3

RESULTS

Baseline Characteristics of Sickle cell Patients

We initially identified a total of 329,525 encounters for 41,105 sickle cell patients of which 9,979 encounters were HbA1c test orders and 296 encounters were fructosamine test orders. After the exclusion of HbA1c and Fructosamine encounters before 2010 and after 2016, we narrowed down the resulting patient cohort to 37151 sickle cell patients of which 526 patients were in TMC (Figure 1). The baseline characteristics of the Sickle cell patients in TMC were similar to the total sickle cell population from all 393 hospitals (Table 2). When the sickle cell patients were distributed based on their diagnosis codes (Table 1), 31032 patients were found to be homozygous HbSS (unspecified, with and without crisis) which represents 83.53% of the entire sickle cell disease population. TMC had a similar profile where 389 patients were homozygous HbSS (unspecified, with and without crisis) which represents 74% of the entire sickle cell disease population. There was a statistically significant association between TMC and the National Hospitals in the case of sickle cell population in the groups of HbSS disease unspecified, HbSS disease without crisis, HbSS disease with crisis, sickle cell/HbC disease without crisis and other sickle cell disease with crisis where $p<0.005$. However, TMC & the national hospitals were independent of each other in the case of the remaining four sickle cell diagnosis groups where $p>0.05$ (Figure 2).

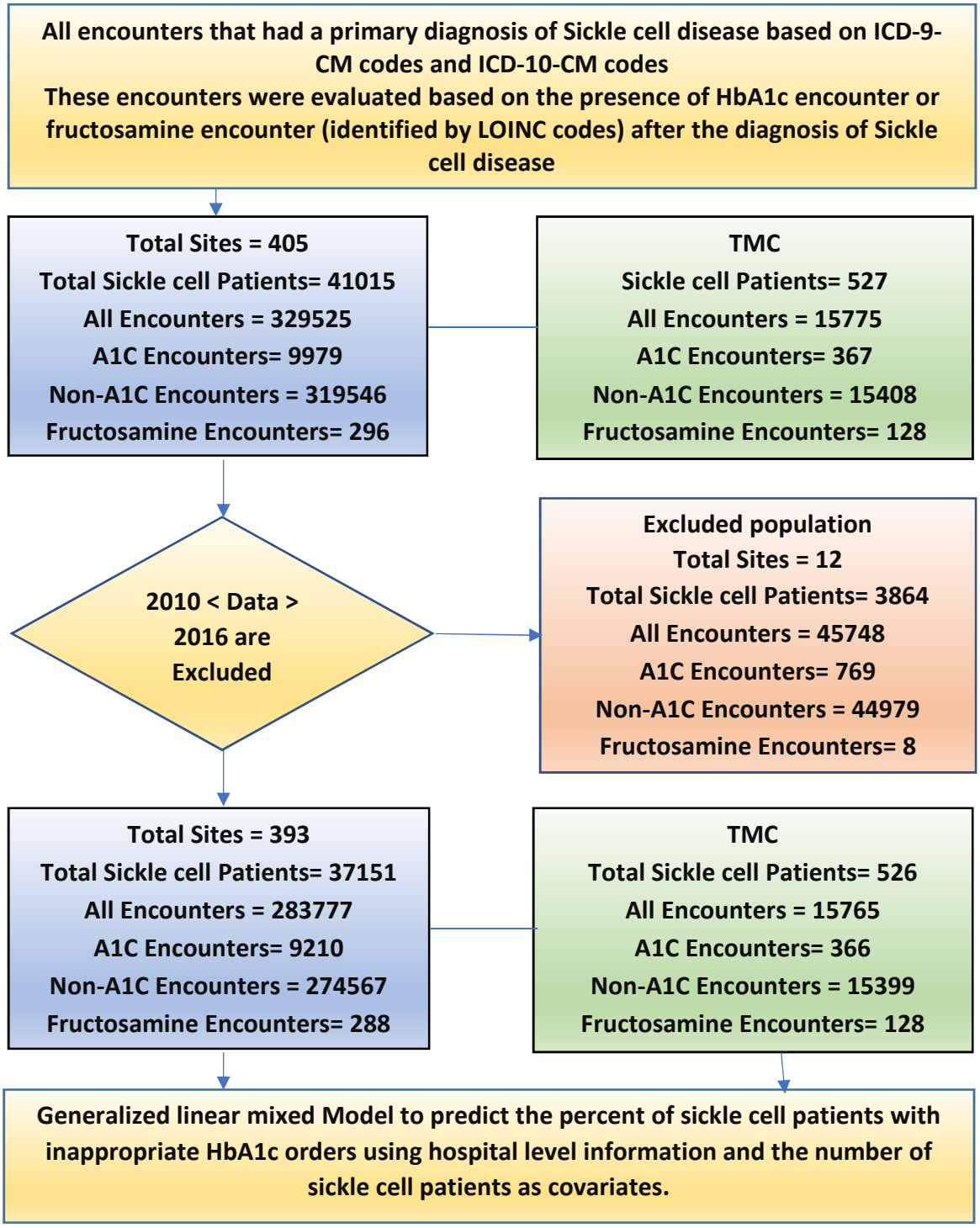

Figure 1. Analysis plan which includes the frequency of the study cohort before and after the exclusion criteria

Table 2: The baseline characteristics of the sickle cell patients from the 393 national facilities compared to the sickle cell patients in TMC

Baseline Characteristics	**All 393 Sites**	**TMC**
Age, years (mean)	32.03 years	36.34
Gender		
Male	16234 (43.81%)	208 (39.54%)
Female	20822 (56.19%)	318 (60.46%)
Race		
African American	23814 (64.10%)	456 (86.69%)
Asian/Pacific	393 (1.06%)	4 (0.76%)
Islander	73 (0.19%)	
Biracial	8948 (24.08%)	31 (5.89%)
Caucasian	142 (0.38%)	1 (0.19%)
Hispanic	3 (0.01%)	
Mid-Eastern	77 (0.21%)	
Indian	2304 (6.2%)	29 (5.51%)
Native American	1370 (3.68%)	5 (0.95%)
Other	27 (0.07%)	

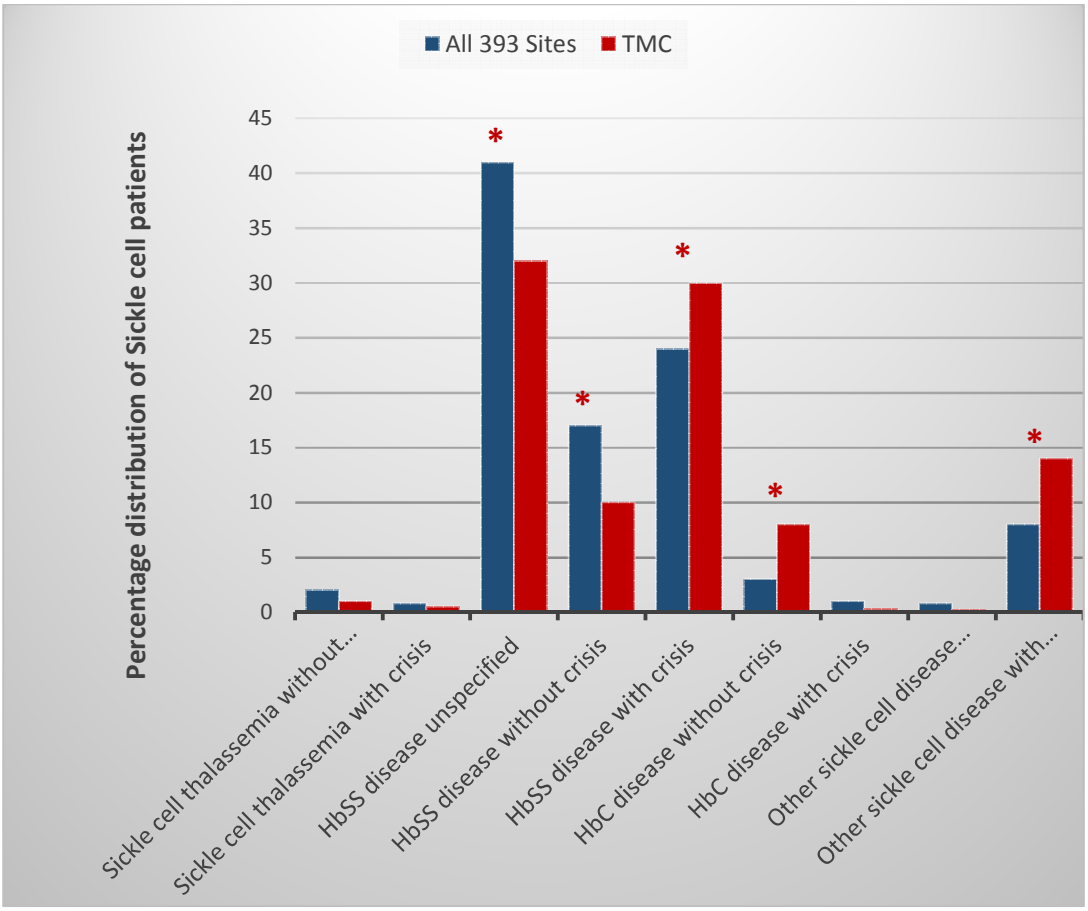

Figure 2. Percentage distribution of Sickle cell patients based on their type of Sickle cell diagnosis in TMC compared to other national facilities. Red * indicates statistically significant groups

HbA1c Encounters in Sickle Cell Population

When the sickle cell patient cohort was analyzed for HbA1c encounters after the diagnosis of sickle cell disease, 11% of the total Sickle cell population (3,927 patients) had at least one HbA1c encounter (Figure 3). However, at TMC 170 patients, almost 32% of the sickle cell population in TMC, had at least one HbA1c encounter (Figure 3). This

shows that the sickle cell population in TMC is tested by HbA1c much more often than compared to their peers. When we broke this down to the annual rate of HbA1c encounters, the sickle cell population in TMC with HbA1c encounters was consistently higher every year when compared to the other national facilities (Figure 4).

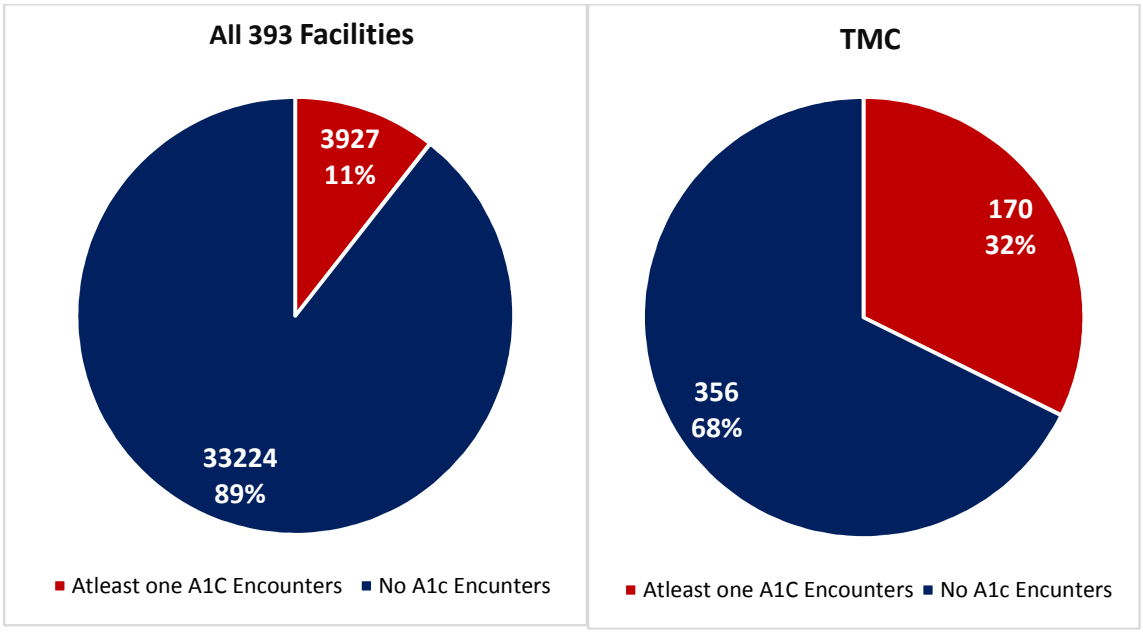

Figure 3. HbA1c encounters of sickle cell patients at all 393 hospitals compared to TMC

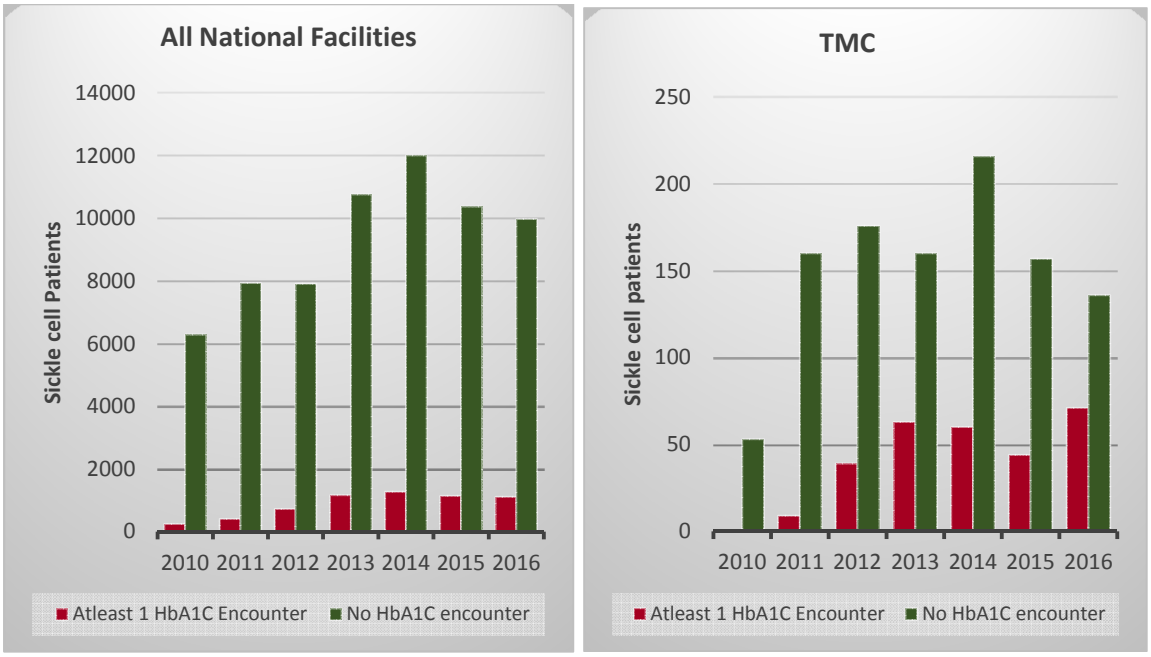

Figure 4. Sickle cell patients with HbA1c encounters per year from 2010 to 2016 at all 393 hospitals compared to TMC

Ranking TMC among other National Facilities

We used the generalized Linear mixed model to rank both the hospitals of TMC (Hospital Hill and Lakewood) against the other national hospitals for the recent years from 2014-2016. Here, each rank of the hospital is calculated based on the ratio of the percentage of HbA1c test ordered for each sickle cell patient per year. From this model (Figure 5), it can be observed that TMC Hospital hill is above the 75% cut-off, and TMC Lakewood is almost near the 75% cut-off mark for all the three years and that both the hospitals are in the bottom 25% quartile with respect to the percentage of inappropriate HbA1c tests when compared to all the other national hospitals. This indicates that this is a potential quality concern which needs to be addressed with sustainable interventions.

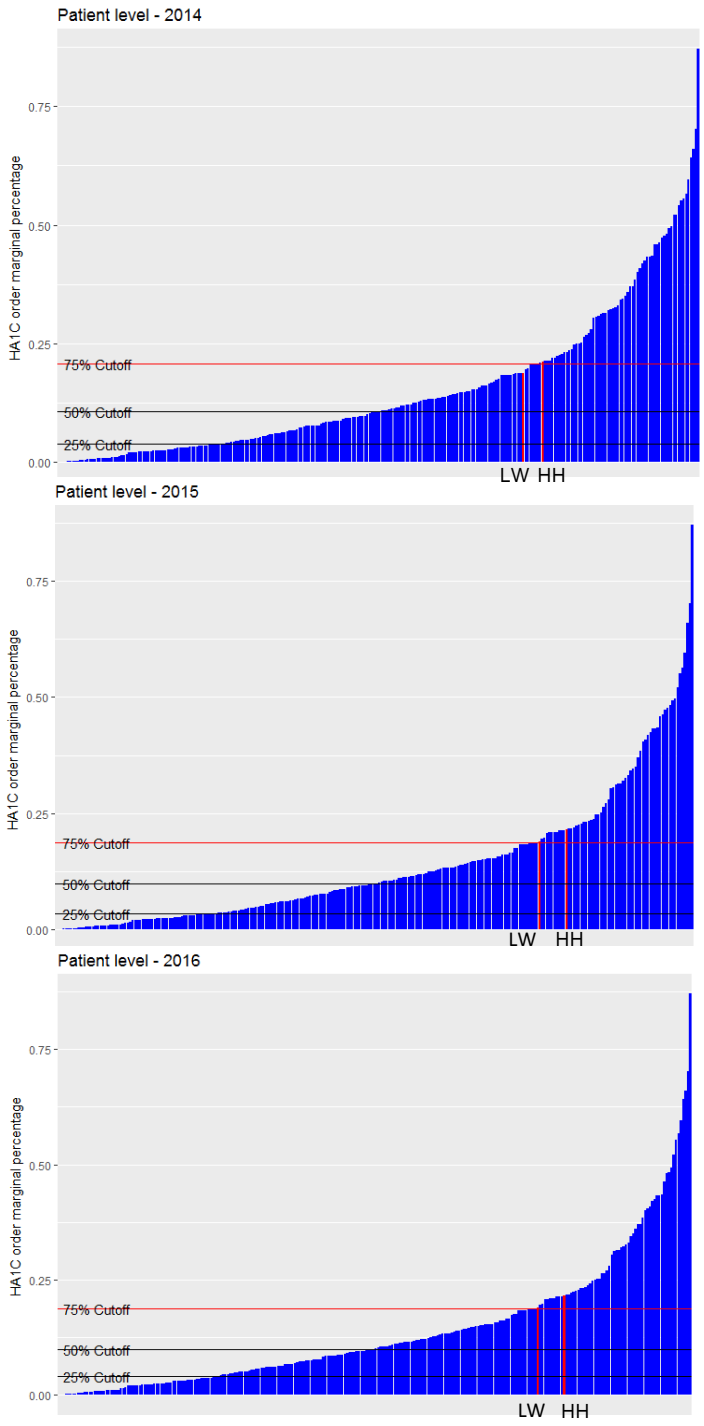

Figure 5. Ranking TMC against other national hospitals based on the linear unbiased predicted percentages from the generalized linear mixed model. Each bar represents one site in that year (Red bar indicates: LW – TMC Lakewood and HH- TMC Hospital Hill)

Fructosamine Encounters in Sickle cell Population

In order to consider whether there were indications of a shift in practice toward more appropriate test ordering, we screened the encounters from the sickle cell cohort for fructosamine orders and found an interesting perspective of the data. There were just 288 Fructosamine encounters in the entire sickle cell population cohort of which 44% of those encounters (128 Fructosamine encounters) were from TMC. There were only 11 hospitals from the sickle cell cohort which had fructosamine encounters and these facilities had 7502 sickle cell patients of which TMC includes 526 sickle cell patients. Excluding TMC, the remaining 10 hospitals have 74 sickle cell patients who had at least one fructosamine encounter while TMC has 10 fold higher sickle cell patient ratio (60 patients) who had at least one fructosamine encounter (Figure 6).

We further mapped out those 134 patients (TMC and the national hospitals) with fructosamine encounters and their hospitals based on their region and compared it with patients with HbA1c encounters in that particular region (Figure 7). From this we can observe that from the entire sickle cell population in the Midwest region (4441 patients) around 20% of them had HbA1c encounters which is almost the same as in the North (29%) and Northeast region (21%). However, the midwest region is the only region where ~2% of sickle cell patients had fructosamine encounters while the rest of the sickle cell population in other regions had very few to no fructosamine encounters.

In order to further investigate the reason behind the high frequency of both HbA1c encounters and Fructosamine encounters in TMC compared to the other national hospitals, we decided to further analyze these 6450 patients in the 10 other national

hospitals where some of them must have both HbA1c and Fructosamine orders. Analyzing the relative order percentage of each test shows that the other 10 hospitals (excluding TMC) have about 3802 sickle cell patients who had either one of those two tests or both. While 98% of those patients had only HbA1c test, 1% had both fructosamine and HbA1c test and 1% had only Fructosamine test (Figure 8). Whereas in TMC, 190 sickle cell patients had either one of those two tests or both and only 68% of them had only HbA1c test while 21% of them had both HbA1c and Frutosamine (Figure 8). This suggests that there might be HbA1c ordering pattern relative to fructosamine test.

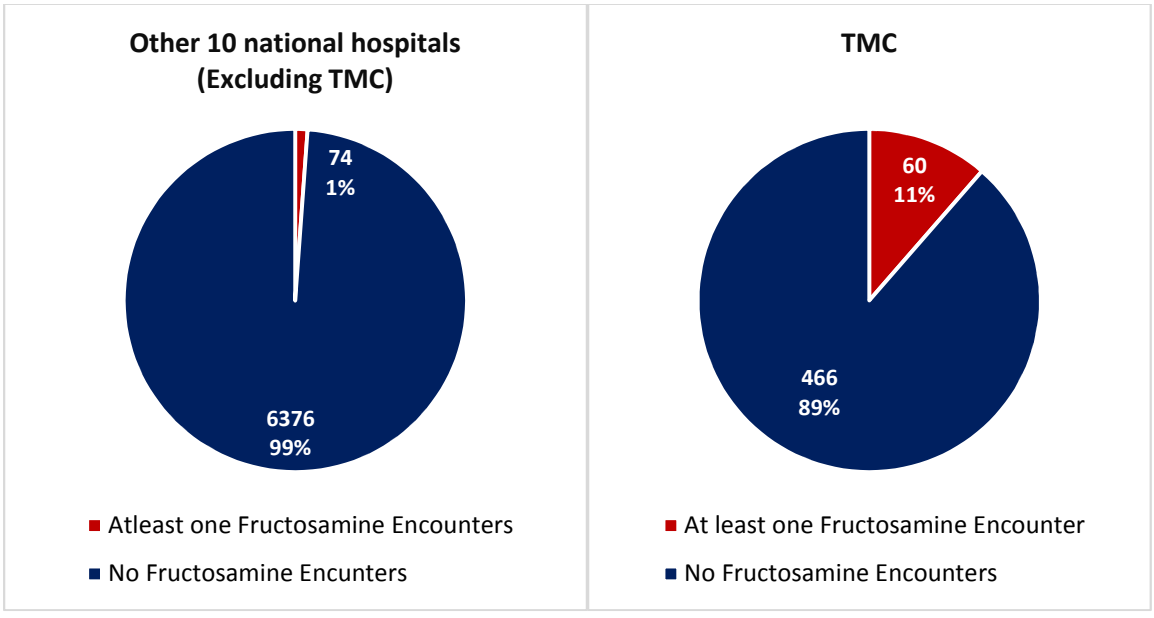

Figure 6. Fructosamine encounters for Sickle cell patients at 10 other national hospitals compared with TMC

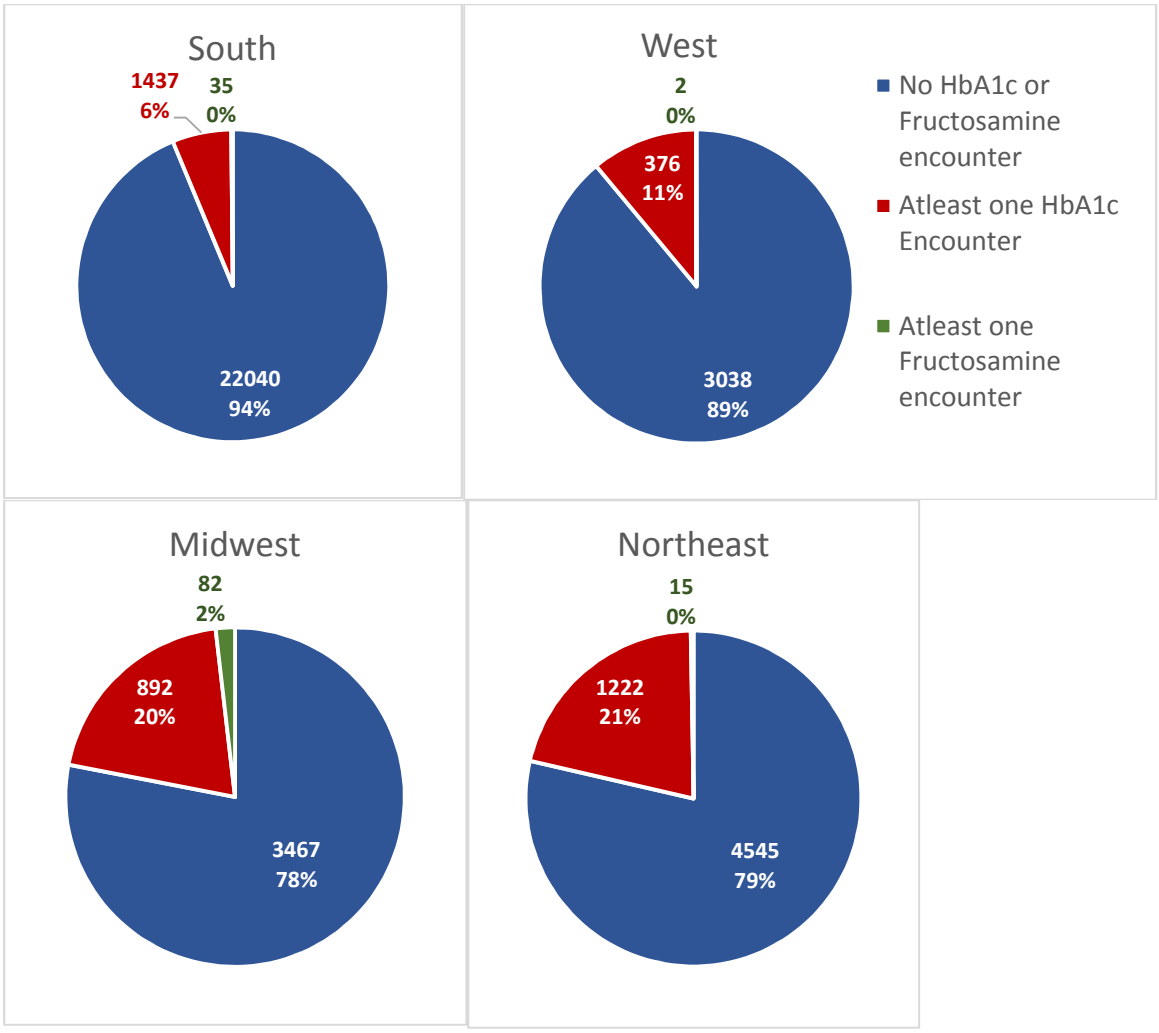

Figure 7. Sickle cell patients mapped according to their US census region and the estimates of their HbA1c orders (red) and Fructosamine orders (green) are given respectively for each region

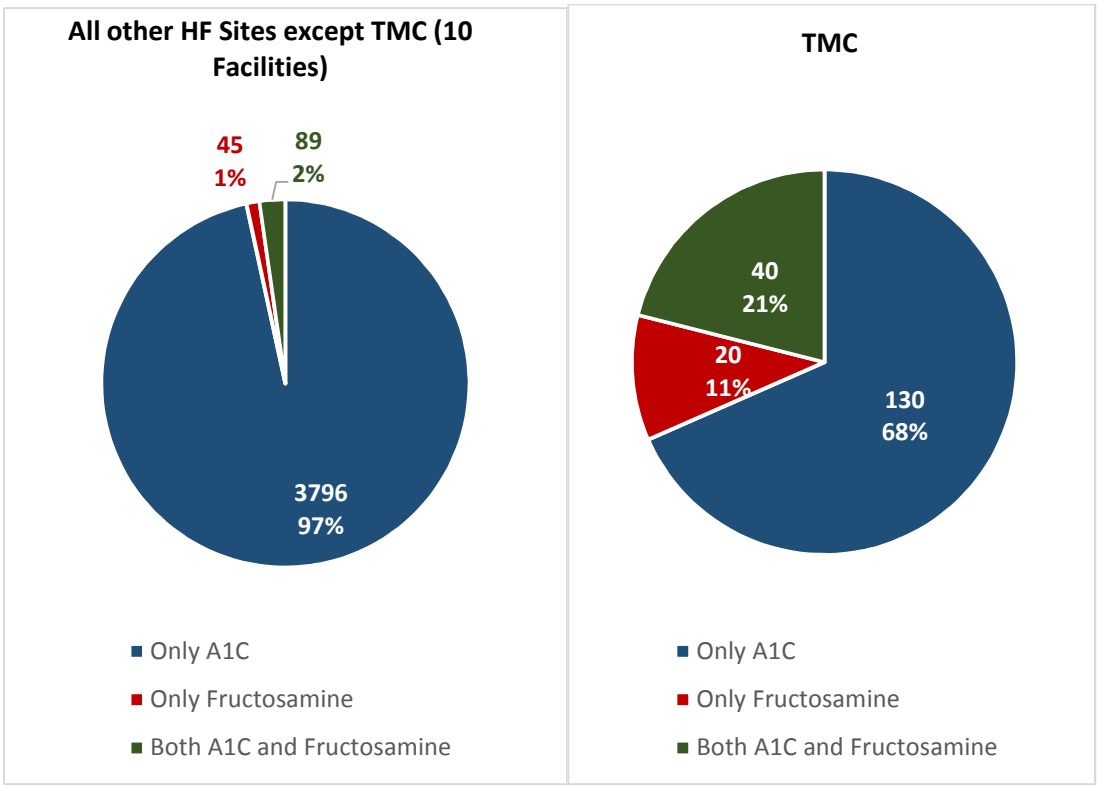

Figure 8. Order percentage of only HbA1c Test, Fructosamine test or both HbA1c and Fructosamine test in 10 other hospitals compared to TMC

Analyzing the timestamp of all the HbA1c encounters and fructosamine encounters associated with the 89 patients (patients in the green subset in Figure 8) who had both fructosamine and HbA1c encounters (410 encounters) in the 10 national facilities other than TMC shows that 62% of those encounters were HbA1c tests that were ordered before the patient was screened with the first fructosamine test and 7% of those encounters were HbA1c and fructosamine tests that were ordered together while 31% of those HbA1c encounters were ordered even after the patients had fructosamine

test (Figure 9). In TMC, the 40 patients (patients in the green subset in TMC in Figure 8) who had both HbA1c and fructosamine tests were analyzed for the HbA1c ordering pattern. It was found that 27% of those 40 patients who had been tested with HbA1c and Fructosamine together was almost three-fold higher when compared to the other 10 national facilities (7% of the sickle cell patients).

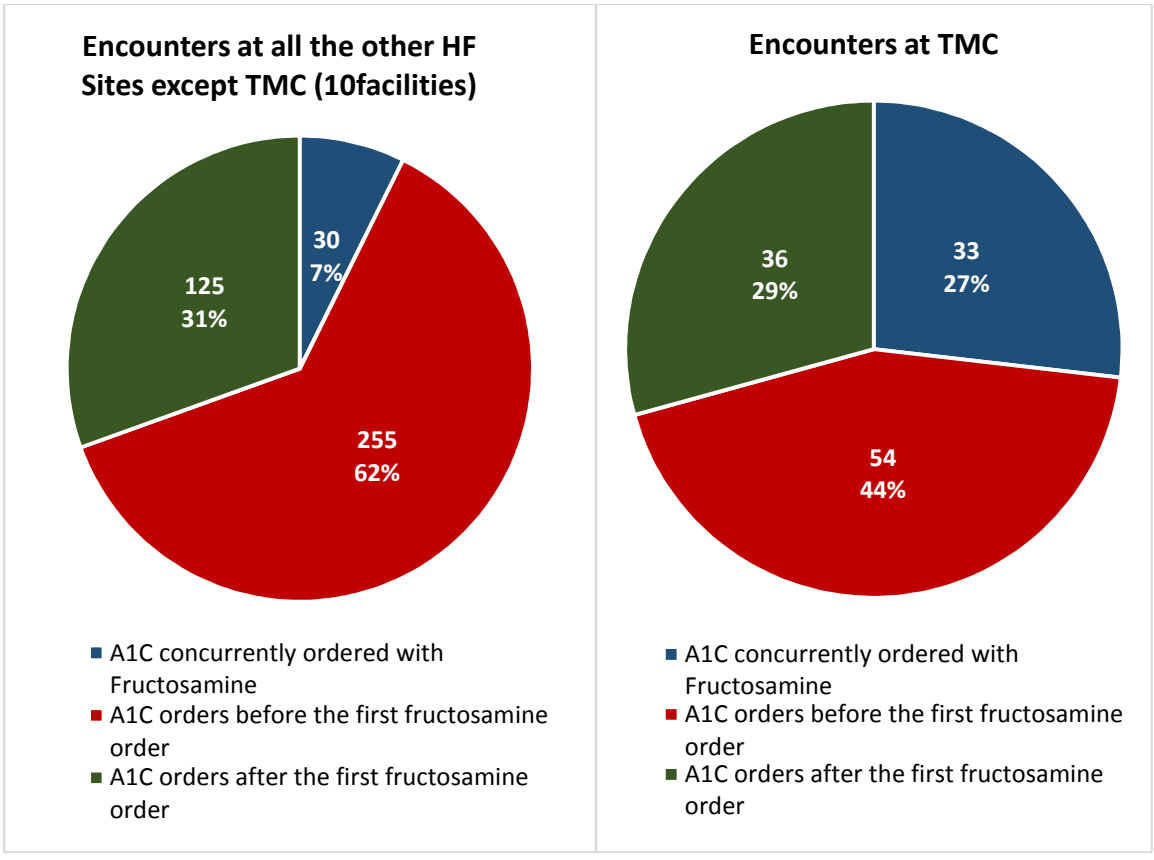

Figure 9: Ordering pattern of HbA1c test relative to Fructosamine test in sickle cell population who had both HbA1c test and Fructosamine test in the 10 national facilities and in TMC

CHAPTER 4

DISCUSSION

The measurement of glycosylated HbA1c is widely accepted as the cornerstone of diagnosis and management of diabetes. However, this test is unreliable for sickle cell disease patients due to their hemoglobin variant and its associated pathological processes including anemia, increased red blood cell turnover, transfusion requirements and increased HbF (Bry et al., 2001). Corrections to some HPLC and cation-exchange methods allow accurate, analytical determination of the glycated hemoglobin in these Sickle cell disease patients (C. W. Weykamp, Penders, Siebelder, Muskiet, & Van der Slik, 1993), however these values impact HbA1c as a marker of long-term glycemic control as the glycated variant hemoglobin has a shorter lifespan. Moreover, there are HbA1c methods which do not report results while some methods flag it as abnormal peaks (Carta, Dall'Olio, & Soffiati, 1997; John, Braconnier, Miedema, Aulesa, & Piras, 1997). Several studies indicate falsely lower level HbA1c values for sickle cell homozygous patients(Gunton & McElduff, 2000; Malekiani, Ganesan, & Decker, 2008; Smaldone, 2008; Tran et al., 2004). Based on these reports, the information campaign and physician's new release sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases stressed the importance of avoiding HbA1c test for Sickle cell disease patients as it might be unreliable ("Sickle cell Trait & Other Hemoglobinopathies & Diabetes (For Providers) | NIDDK," 2016). The National Glycohemoglobin Standardization Program, supported by the National Institute of Diabetes and Digestive and Kidney Diseases and Centers for Disease Control and Prevention, has standardized

the measurements of HbA1c in laboratories in patients with HbS trait and HbC variant. However, for patients with homozygous sickle cell condition, they caution against the use of HbA1c test and propose other alternative tests glycated serum protein or glycated albumin which can be considered for these patients("NGSP: Factors that Interfere with HbA1c Test Results," 2016). Based on these two reports, The Center for Disease Control and Prevention had also released information for providers to not use HbA1c test for Sickle cell trait patients and other hemoglobinopathies as it might falsely lower HbA1c values(CDC, 2017). Futhermore, ADA has acknowledged that in patients with Sickle cell disease, in whom HbA1c is unreliable due to the altered red cell turnover, the assessment of other indices of chronic glycemia may be advisable(ADA, 2014).

The prior reports provided local analysis of this ordering practice. However, there has been no national level analysis to set a baseline characteristic of inappropriate HbA1c orders for sickle cell disease patients. Our work is unique in that we have a population wide look for this ordering practice using HIPAA compliant, de-identified national data warehouse, Cerner's Health Facts database. And, used this as a baseline in evaluating this quality concern of inappropriate HbA1c orders in Truman Medical Centers. Results (Figure 10) show that TMC when compared to the national hospital cohort had a higher percentage of Sickle cell patients with HbA1c tests (32% versus 11%). Ranking the linear unbiased predicted percentages of all the hospitals show that TMC ranks in the bottom 25% quartile when compared to the other national hospitals with respect to inappropriate HbA1c orders. However, TMC when compared to the national hospital cohort had a higher percentage of sickle cell patients with Fructosamine tests (11% versus 1%). This

high percentage of fructosamine encountered sickle cell patients in TMC is because 67% of those fructosamine encountered patients had both HbA1c tests and fructosamine. This correlates with the finding that fructosamine encounters have significantly increased after the year 2014. However, there was still a significantly higher number of sickle cell disease patients in TMC than in other national hospitals who had only HbA1c tests (24% versus 10%). This suggests that TMC being in the bottom quartile signifies that inappropriate HbA1c orders in sickle cell patients is a major quality concern in TMC when compared to its peers. This potential quality concern in TMC needs to be addressed with sustainable interventions in such a way that the physician is aware of the sickle cell condition of the patient before ordering HbA1c test. And the fact that, the use of a fructosamine test (glycated serum protein) in patients with sickle cell disease as a standalone test or in combination with HbA1c may be a reasonable option when an accurate HbA1c test cannot be obtained.

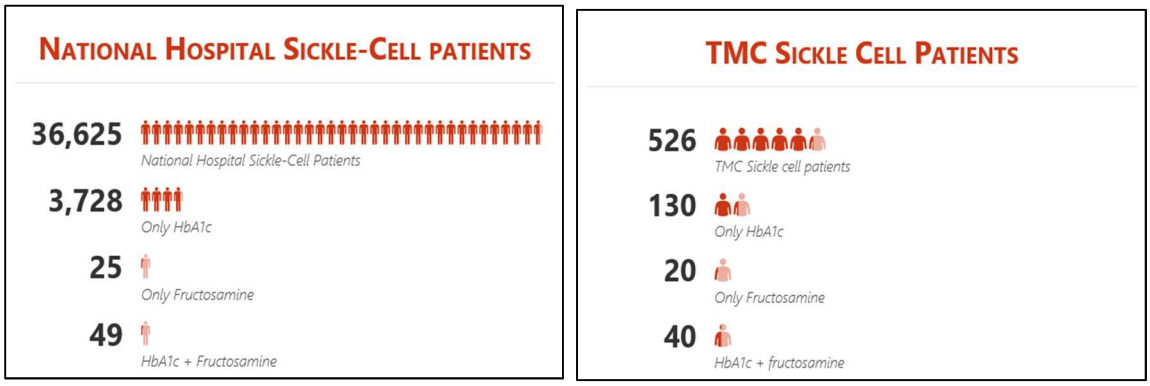

Figure 10. Summary of the key findings in the Sickle cell population in other national hospitals (excluding TMC) compared to the Sickle cell population in TMC

Our study has several strengths. It is based on a large sample from multiple hospitals across US. This has an advantage over other local analyses, on the fact that this study can examine selected conditions and set a baseline characteristic for the quality concern. It also makes use of both ICD-9-CM and ICD-10-CM diagnosis codes which can efficiently capture the sickle cell disease patients. We used a Practice Based Evidence (PBE) approach which is an integral aspect of the Institute of Medicine (IOM) Learning Healthcare System strategy and can be performed by analyzing data generated during the delivery of the patient care (Ammerman et al., 2014). Often QI projects are selected in reaction to a recent adverse event. While this is frequently necessary after a critical issue, it may also result in failure to recognize deeper systemic quality gaps in which an organization is at significant variance from their peers. With respect to laboratory quality improvement, there is a significant opportunity to apply the practice based evidence strategy to the recognition of quality gaps, the selection of critical quality improvement projects and comparison with facilities with a high and low frequencies of the quality gap in order to inform interventions (Green, 2008). The proposed Generalized Linear Mixed Model (GLMM) in this study offered a few advantages. First, the linear unbiased predicted percentages from GLMM adjusted the bias due to covariates. Second, GLMMs were able to model the longitudinal structure of the data. Third, by including the hospital as a random variable in the mixed model, we were able to generalize the inference of the fixed effect to the population. Finally, the analytic pipeline developed in this study can be easily adopted to different measurements of outcome variables and address different research questions from Health Fact data source.

Conversely, this study has a number of significant limitations. First, this large national database of clinical data contains valuable yet heterogenous and difficult data in terms of high dimensionality. Additionally, analyzing EHR data is more challenging when compared to carefully controlled clinical trials as the data in the Health Facts data warehouse is completely reliant on billing codes with no way to verify its accuracy. Finally, fructosamine is rarely used in clinical practice and therefore the national data warehouse had very few encounters which can be compared with TMC. Other alternative tests such as glycated albumin and 1,5 anhydroglucitol did not have any encounters in the Sickle cell population in the EHR and was therefore not evaluated.

Future studies, involving the diagnosis of diabetes mellitus in Sickle cell patients with HbA1c test would be challenging yet would result in a more precise dataset that provides more granularity. More granularity in the dataset could make connections in identifying incorrect diabetes diagnoses for sickle cell patients with inappropriate HbA1c tests and provide more details on possible mechanisms. Additionally, implementing a sustainable intervention in such a way that physicians are aware of this quality concern in ordering inappropriate HbA1c tests and then repeating the baseline measures could provide a way to identify if the quality concern has been alleviated.

This project utilized the data from the HIPAA compliant, electronic health record (EHR) data in the Cerner Health Facts ™ (HF) data warehouse related to the clinical utility of the glycated Hemoglobin (HbA1c) test to monitor diabetes for sickle cell disease patients. Ranking the unbiased linear percentages estimated from the Generalized Linear Mixed Model of all the hospitals show that TMC ranks in the bottom 25% quartile

when compared to the other national hospitals. These findings indicate that inappropriate HbA1c orders in sickle cell patients is a potential quality concern in TMC which needs to be addressed with sustainable interventions so that overtreatment or under-treatment of the diabetic condition in sickle cell disease patients are avoided in order to improve patient and organizational outcome.

REFERENCES

Ammerman, A., Smith, T. W., & Calancie, L. (2014). Practice-based evidence in public health: Improving reach, relevance, and results. *Annual Review of Public Health*, *35*(1), 47–63. https://doi.org/10.1146/annurev-publhealth-032013-182458

Association, A. D. (2014). Standards of medical care in diabetes—2014. *Diabetes Care*, *37*(Supplement 1), S14–S80.

Baker, J. R., Metcalf, P. A., Holdaway, I. M., & Johnson, R. N. (1985). Serum fructosamine concentration as measure of blood glucose control in type I (insulin dependent) diabetes mellitus. *British Medical Journal (Clinical Research Ed.)*, *290*(6465), 352–355.

Baker, J. R., Metcalf, P. A., Johnson, R. N., Newman, D., & Rietz, P. (1985). Use of protein-based standards in automated colorimetric determinations of fructosamine in serum. *Clinical Chemistry*, *31*(9), 1550–1554.

Baker, J. R., O'Connor, J. P., Metcalf, P. A., Lawson, M. R., & Johnson, R. N. (1983). Clinical usefulness of estimation of serum fructosamine concentration as a screening test for diabetes mellitus. *British Medical Journal (Clinical Research Ed.)*, *287*(6396), 863–867.

Blumenthal, D., & Tavenner, M. (2010). The "meaningful use" regulation for electronic health records. *New England Journal of Medicine*, *363*(6), 501–504. https://doi.org/10.1056/NEJMp1006114

Bry, L., Chen, P. C., & Sacks, D. B. (2001). Effects of hemoglobin variants and chemically modified derivatives on assays for glycohemoglobin. *Clinical Chemistry*, *47*(2), 153–163.

Camargo, J. L., & Gross, J. L. (2004). Glycohemoglobin (GHb): Clinical and analytical aspects. *Arquivos Brasileiros de Endocrinologia & Metabologia*, *48*(4), 451–463.

Carta, M., Dall'Olio, G., & Soffiati, G. (1997). Determination of HbA1c in the presence of haemoglobin variants: Comparison of three HPLC techniques. *European Journal of Clinical Chemistry and Clinical Biochemistry*, *35*(12), 923–925.

CDC. (2016, August 31). *Data and Statistics* | Sickle cell Disease | NCBDDD | CDC. Retrieved February 11, 2018, from https://www.cdc.gov/ncbddd/sicklecell/data.html

CDC. (2017, October 4). *Sickle cell Disease* | NCBDDD | CDC. Retrieved March 11, 2018, from https://www.cdc.gov/ncbddd/sicklecell/index.html

Cohen, R. M., Holmes, Y. R., Chenier, T. C., & Joiner, C. H. (2003). Discordance between HbA1c and fructosamine: Evidence for a glycosylation gap and its relation to diabetic nephropathy. *Diabetes Care*, *26*(1), 163–167.

El-Agouza, I., Abu Shahla, A., & Sirdah, M. (2002). The effect of iron deficiency anaemia on the levels of haemoglobin subtypes: Possible consequences for clinical diagnosis. *Clinical and Laboratory Haematology*, *24*(5), 285–289.

Elmariah, H., Garrett, M. E., De Castro, L. M., Jonassaint, J. C., Ataga, K. I., Eckman, J. R., Telen, M. J. (2014). Factors associated with survival in a contemporary adult

Sickle cell disease cohort. *American Journal of Hematology*, *89*(5), 530–535. https://doi.org/10.1002/ajh.23683

Elson, R. B., & Connelly, D. P. (1995). Computerized patient records in primary care: Their role in mediating guideline-driven physician behavior change. *Archives of Family Medicine*, *4*(8), 698.

Global Burden of Disease Study 2013 Collaborators. (2015). Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: A systematic analysis for the Global Burden of Disease Study 2013. *Lancet (London, England)*, *386*(9995), 743–800. https://doi.org/10.1016/S0140-6736(15)60692-4

Green, L. W. (2008). Making research relevant: If it is an evidence-based practice, where's the practice-based evidence? *Family Practice*, *25 Suppl 1*, i20-24. https://doi.org/10.1093/fampra/cmn055

Gunton, J. E., & McElduff, A. (2000). Hemoglobinopathies and HbA (1c) measurement. *Diabetes Care*, *23*(8), 1197.

Hillestad, R., Bigelow, J., Bower, A., Girosi, F., Meili, R., Scoville, R., & Taylor, R. (2005). Can electronic medical record systems transform health care? Potential health benefits, savings, and costs. *Health Affairs*, *24*(5), 1103–1117.

Hoerbst, A., & Ammenwerth, E. (2010). Electronic health records. *Methods of Information in Medicine*, *49*(04), 320–336.

Jeffcoate, S. L. (2004). Diabetes control and complications: The role of glycated haemoglobin, 25 years on. *Diabetic Medicine: A Journal of the British Diabetic Association*, *21*(7), 657–665. https://doi.org/10.1046/j.1464-5491.2003.01065.x

Jiao, Y., Okumiya, T., Saibara, T., Park, K., & Sasaki, M. (1998). Abnormally decreased HbA1c can be assessed with erythrocyte creatine in patients with a shortened erythrocyte age. *Diabetes Care*, *21*(10), 1732–1735.

John, W. G., Braconnier, F., Miedema, K., Aulesa, C., & Piras, G. (1997). Evaluation of the menarini–arkray HA 8140 hemoglobin A1c analyzer. *Clinical Chemistry*, *43*(6), 968–975.

Johnston, M. E., Langton, K. B., Haynes, R. B., & Mathieu, A. (1994). Effects of computer-based clinical decision support systems on clinician performance and patient outcome: A critical appraisal of research. *Annals of Internal Medicine*, *120*(2), 135–142.

Juraschek, S. P., Steffes, M. W., & Selvin, E. (2012). Associations of alternative markers of glycemia with hemoglobin A(1c) and fasting glucose. *Clinical Chemistry*, *58*(12), 1648–1655. https://doi.org/10.1373/clinchem.2012.188367

Kawano, K. (1999). Quality control, quality assessment of laboratory tests, HbA1c. *The Southeast Asian Journal of Tropical Medicine and Public Health*, *30*, 117–121.

Kirby, J. C., Speltz, P., Rasmussen, L. V., Basford, M., Gottesman, O., Peissig, P. L., … Denny, J. C. (2016). PheKB: A catalog and workflow for creating electronic phenotype algorithms for transportability. *Journal of the American Medical*

Informatics Association: JAMIA, *23*(6), 1046–1052. https://doi.org/10.1093/jamia/ocv202

Ko, G. T., Chan, J. C., Yeung, V. T., Chow, C. C., Tsang, L. W., Li, J. K., Cockram, C. S. (1998). Combined use of a fasting plasma glucose concentration and HbA1c or fructosamine predicts the likelihood of having diabetes in high-risk subjects. *Diabetes Care*, *21*(8), 1221–1225.

Kohne, E. (2011). Hemoglobinopathies. *Deutsches Ärzteblatt International*, *108*(31–32), 532–540. https://doi.org/10.3238/arztebl.2011.0532

Lacy, M. E., Wellenius, G. A., Sumner, A. E., Correa, A., Carnethon, M. R., Liem, R. I., … Wu, W.-C. (2017). Association of Sickle cell trait with hemoglobin a1c in African Americans. *JAMA*, *317*(5), 507–515. https://doi.org/10.1001/jama.2016.21035

Lenters-Westra, E., Schindhelm, R. K., Bilo, H. J., & Slingerland, R. J. (2013). Haemoglobin A1c: Historical overview and current concepts. *Diabetes Research and Clinical Practice*, *99*(2), 75–84. https://doi.org/10.1016/j.diabres.2012.10.007

Lippi, G., & Targher, G. (2010). Glycated hemoglobin (HbA1c): Old dogmas, a new perspective? *Clinical Chemistry and Laboratory Medicine*, *48*(5), 609–614.

Lippi, G., & Targher, G. (2011). A laboratory standpoint on the role of hemoglobin A1c for the diagnosis of diabetes in childhood: More doubts than certainties? *Pediatric Diabetes*, *12*(3 Pt 1), 183–186. https://doi.org/10.1111/j.1399-5448.2010.00684.x

Malekiani, C. L., Ganesan, A., & Decker, C. F. (2008). Effect of hemoglobinopathies on hemoglobin A1c measurements. *The American Journal of Medicine*, *121*(6), e5.

Malmström, H., Walldius, G., Grill, V., Jungner, I., Gudbjörnsdottir, S., & Hammar, N. (2014). Fructosamine is a useful indicator of hyperglycaemia and glucose control in clinical and epidemiological studies – cross-sectional and longitudinal experience from the amoris cohort. *PLoS ONE*, *9*(10), e111463. https://doi.org/10.1371/journal.pone.0111463

Michalik, D. E., Taylor, B. W., & Panepinto, J. A. (2017). Identification and validation of a Sickle cell disease cohort within electronic health records. *Academic Pediatrics*, *17*(3), 283–287. https://doi.org/10.1016/j.acap.2016.12.005

Miller, R. H., & Sim, I. (2004). Physicians' use of electronic medical records: Barriers and solutions. *Health Affairs*, *23*(2), 116–126.

NIDDK. *Sickle cell Trait & Other Hemoglobinopathies & Diabetes (For Providers)*. (n.d.). Retrieved February 16, 2018, from https://www.niddk.nih.gov/health-information/diagnostic-tests/Sickle cell-trait-hemoglobinopathies-diabetes

NGSP. *Factors that Interfere with HbA1c Test Results*. (n.d.). Retrieved May 24, 2017, from http://www.ngsp.org/factors.asp

Patrinos, G.P., B. Giardine, C. Riemer, W. Miller, D.H.K. Chui, N.P. Anagnou, H. Wajcman, & R.C. Hardison. (2004). Improvements in the HbVar database of human hemoglobin variants and thalassemia mutations for population and sequence variation studies [Database issue: D537-541]. Retrieved February 15, 2018, from http://globin.cse.psu.edu/hbvar/menu.html

Piel, F. B., Patil, A. P., Howes, R. E., Nyangiri, O. A., Gething, P. W., Dewi, M., … Hay, S. I. (2013). Global epidemiology of sickle haemoglobin in neonates: A

contemporary geostatistical model-based map and population estimates. *Lancet*, *381*(9861), 142–151. https://doi.org/10.1016/S0140-6736(12)61229-X

Piel, F. B., Patil, A. P., Howes, R. E., Nyangiri, O. A., Gething, P. W., Williams, T. N., … Hay, S. I. (2010). Global distribution of the Sickle cell gene and geographical confirmation of the malaria hypothesis. *Nature Communications*, *1*, 104.

Powars, D. R., Chan, L. S., Hiti, A., Ramicone, E., & Johnson, C. (2005). Outcome of Sickle cell anemia: a 4-decade observational study of 1056 patients. *Medicine*, *84*(6), 363–376.

Rees, D. C., Williams, T. N., & Gladwin, M. T. (2010a). Sickle cell disease. *The Lancet*, *376*(9757), 2018–2031.

Rondeau, P., & Bourdon, E. (2011). The glycation of albumin: Structural and functional impacts. *Biochimie*, *93*(4), 645–658. https://doi.org/10.1016/j.biochi.2010.12.003

Roohk, H. V., & Zaidi, A. R. (2008). A review of glycated albumin as an intermediate glycation index for controlling diabetes. *Journal of Diabetes Science and Technology (Online)*, *2*(6), 1114–1121.

Sacks, D. B. (2012). Measurement of Hemoglobin A1c: A new twist on the path to harmony. *Diabetes Care*, *35*(12), 2674–2680.

Schabenberger, O. (2005). Introducing the GLIMMIX procedure for generalized linear mixed models. *SUGI 30 Proceedings*, *196*.

Schnedl, W. J., Krause, R., Halwachs-Baumann, G., Trinker, M., Lipp, R. W., & Krejs, G. J. (2000). Evaluation of HbA1c determination methods in patients with hemoglobinopathies. *Diabetes Care*, *23*(3), 339–344.

Selvin, E., Rawlings, A. M., Grams, M., Klein, R., Sharrett, A. R., Steffes, M., & Coresh, J. (2014). Fructosamine and glycated albumin for risk stratification and prediction of incident diabetes and microvascular complications: A prospective cohort analysis of the Atherosclerosis Risk in Communities (ARIC) study. *The Lancet. Diabetes & Endocrinology*, *2*(4), 279–288. https://doi.org/10.1016/S2213-8587(13)70199-2

Smaldone, A. (2008). Glycemic control and hemoglobinopathy: When A1C may not be reliable. *Diabetes Spectrum*, *21*(1), 46–49. https://doi.org/10.2337/diaspect.21.1.46

Smith, M., Halvorson, G., & Kaplan, G. (2012). What's needed is a health care system that learns: Recommendations from an IOM report. *JAMA*, *308*(16), 1637–1638. https://doi.org/10.1001/jama.2012.13664

Speeckaert, M., Van Biesen, W., Delanghe, J., Slingerland, R., Wiecek, A., Heaf, J., … European renal best practice guideline development group on diabetes in advanced CKD. (2014). Are there better alternatives than haemoglobin A1c to estimate glycaemic control in the chronic kidney disease population? *Nephrology, Dialysis, Transplantation: Official Publication of the European Dialysis and Transplant Association - European Renal Association*, *29*(12), 2167–2177. https://doi.org/10.1093/ndt/gfu006

Strack, B., Deshazo, J., Gennings, C., Olmo Ortiz, J. L., Ventura, S., Cios, K., & N Clore, J. (2014). Impact of HbA1c measurement on hospital readmission rates: Analysis

of 70,000 clinical database patient records. *BioMed Research International*, *2014*, 781670. https://doi.org/10.1155/2014/781670

Tran, H. A., Silva, D., & Petrovsky, N. (2004). Case study: Potential pitfalls of using hemoglobin A1c as the sole measure of glycemic control. *Clinical Diabetes*, *22*(3), 141–143.

True, M. W. (2009). Circulating biomarkers of glycemia in diabetes management and implications for personalized medicine. *Journal of Diabetes Science and Technology*, *3*(4), 743–747. https://doi.org/10.1177/193229680900300421

Uzu, T., Hatta, T., Deji, N., Izumiya, T., Ueda, H., Miyazawa, I., … Arimura, T. (2009). Target for glycemic control in type 2 diabetic patients on hemodialysis: Effects of anemia and erythropoietin injection on hemoglobin A(1c). *Therapeutic Apheresis and Dialysis: Official Peer-Reviewed Journal of the International Society for Apheresis, the Japanese Society for Apheresis, the Japanese Society for Dialysis Therapy*, *13*(2), 89–94. https://doi.org/10.1111/j.1744-9987.2009.00661.x

Wang, S. J., Middleton, B., Prosser, L. A., Bardon, C. G., Spurr, C. D., Carchidi, P. J., … Sussman, A. J. (2003). A cost-benefit analysis of electronic medical records in primary care. *The American Journal of Medicine*, *114*(5), 397–403.

Ware, R. E., Montalembert, M. de, Tshilolo, L., & Abboud, M. R. (2017). Sickle cell disease. *The Lancet*, *390*(10091), 311–323. https://doi.org/10.1016/S0140-6736(17)30193-9

Weatherall, D. J., & Clegg, J. B. (2001). Inherited haemoglobin disorders: An increasing global health problem. *Bulletin of the World Health Organization*, *79*(8), 704–712.

Weykamp, C., John, W. G., & Mosca, A. (2009). A review of the challenge in measuring hemoglobin A1c. *Journal of Diabetes Science and Technology*, *3*(3), 439–445. https://doi.org/10.1177/193229680900300306

Weykamp, C. W., Penders, T. J., Muskiet, F. A., & van der Slik, W. (1993). Influence of hemoglobin variants and derivatives on glycohemoglobin determinations, as investigated by 102 laboratories using 16 methods. *Clinical Chemistry*, *39*(8), 1717–1723.

Weykamp, C. W., Penders, T. J., Siebelder, C. W., Muskiet, F. A., & Van der Slik, W. (1993). Interference of carbamylated and acetylated hemoglobins in assays of glycohemoglobin by HPLC, electrophoresis, affinity chromatography, and enzyme immunoassay. *Clinical Chemistry*, *39*(1), 138–142.

Whiting, D. R., Guariguata, L., Weil, C., & Shaw, J. (2011). IDF diabetes atlas: Global estimates of the prevalence of diabetes for 2011 and 2030. *Diabetes Research and Clinical Practice*, *94*(3), 311–321. https://doi.org/10.1016/j.diabres.2011.10.029

VITA

Shivani Sivasankar was born March 22, 1995 in Chennai, India. She was primarily educated in St.Columban's Anglo Indian Higher Secondary School, and graduated from High School in 2012. She graduated in 2016 from Anna University in India with Bachelors of Technology degree in Biotechnology. She was awarded the 14th rank among 731 candidates who graduated in the Biotechnology program. She also worked as a Bioinformatics Associate in Biozone Research Technologies and Sankara Netheralaya.

In August 2016, she began a Master of Science in Bioinformatics degree with emphasis on Genomics through the Biomedical and Health Informatics Department at University of Missouri-Kansas City School of Medicine. While at UMKC, she worked as a Graduate Research Assistant on quality improvement projects funded by the CDC grant. Upon completion of her degree requirements, Shivani plans to pursue Ph.D. in Bioinformatics to continue to explore and learn new things.