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SCHOOL OF MEDICINE

Thesis

A RETROSPECTIVE ASSESSMENT OF ROUTINE RENAL FUNCTION SCREENING IN PATIENTS WITH SICKLE CELL DISEASE

by

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A RETROSPECTIVE ASSESSMENT OF ROUTINE RENAL FUNCTION SCREENING IN PATIENTS WITH SICKLE CELL DISEASE

JUSTIN PAUL KITTREDGE

ABSTRACT

BACKGROUND

Routine renal screens are essential to the healthcare maintenance of pediatric patients with sickle cell disease. There is an inadequate amount of evidence, however, to support a universal standardized practice. As a result, sickle cell patients are subject to significant variability in care. The objective of this study was to assess the practice of routine renal screens at Boston Children's Hospital.

METHODS

We performed a chart review of 330 total patients from 2011 through 2013 to analyze the performance of microalbumin renal screens and urinalyses at routine clinic visits. With this data, we evaluated the institution's compliance with its adopted renal screening guidelines, examined renal screening variability across patient demographics and among providers, and compared the performance of different laboratory measures.

RESULTS

Renal screens were performed in 34.2% of the eligible study population. There were no statistically significant differences in the performance of renal screens across patient age, sickle phenotype or disease-modifying therapy. Patients aged from 5-9 years old, however, demonstrated a non-significant trend toward a lower frequency of successful

renal screens. The percentage of samples collected for microalbumin excretion within the female cohort was significantly higher than the institutional average (41.7% vs 34.2%, p = 0.024) and significantly lower within the male population (27.6% vs 34.2%, p = 0.034). The performance of renal screens varied significantly from one provider to another. In all areas of analysis, the frequency of urinalyses performed was similar to the frequency of microalbumin excretion rates.

CONCLUSION

This study suggests that providers are not routinely adhering to the institutional standard for renal screens. There remains little insight into providers' basis of renal screen practice: providers may not be cognizant of the institution's practice guidelines or may not consider early detection of microalbuminuria essential to the healthcare maintenance in patients with sickle cell disease. Future studies are warranted to fully comprehend the low frequency of renal screens performed in pediatric sickle cell patients.

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LIST OF ABBREVIATIONS

ACE.....Angiotensin-Converting Enzyme

ARBs.....Angiotensin type II Receptor Blockers

BCH .....Boston Children's Hospital

CKD ..... Chronic Kidney Disease

CSSCD..... Cooperative Study of Sickle Cell Disease

ESD.....Extreme Studentized Deviate

ESRD ..... End Stage Renal Disease

GFR.....Glomerular Filtration Rate

Hb.....Hemoglobin

HbAS..... Sickle Cell Trait

HbS .....Sickle Hemoglobin

MA .....Microalbumin

NEPSCC .....New England Pediatric Sickle Cell Consortium

RBC.....Red Blood Cell

RBF ..... Renal Blood Flow

SCA..... Sickle Cell Anemia

SCD..... Sickle Cell Disease

SCN.....Sickle Cell Nephropathy

UA.....Urinalysis

UACR .....Urine Albumin-to-Creatinine Ratio

INTRODUCTION

Sickle cell disease (SCD) describes a group of autosomal recessive disorders that are caused by point mutations in the sixth codon of the β-globin gene. In the most common anomaly, hydrophilic glutamic acid is replaced with hydrophobic valine, resulting in the formation of sickle hemoglobin (HbS) (**Figures 1** and **2**). There are multiple combinations of abnormal hemoglobins resulting in SCD phenotypes. All contain at least one sickle gene (HbS). Inheritance of the sickle gene from both parents leads to the homozygous HbSS disease, otherwise known as Sickle Cell Anemia (SCA). In addition to SCA, there are three other common heterozygote phenotypes linked to SCD, all with variable clinical severity (**Table 1**). The sickle cell gene has profound impacts on the red blood cell (RBC) and the patient's overall well-being. Hemoglobin is the protein in the RBC responsible for transporting oxygen from the lungs to the rest of the body. High concentrations of HbS polymerize when oxygen is released, causing sickling in the RBC. Normally pliable and biconcave-shaped RBCs become rigid and sickle shaped (**Figure 3**). This results in increased red cell hemolysis, adhesion of sickled cells to vascular endothelium, and thus occlusion of small vasculature that impairs blood supply and function of multiple organs (**Figure 4**).

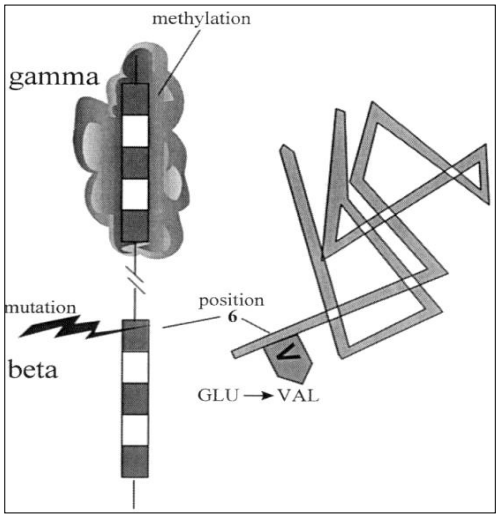

Figure 1. **Hb-Beta mutation.** A single point mutation in the 147 amino acid polypeptide chain of Hb-Beta results in the formation of HbS (1).

Figure 2: **Abnormal SCD Hemoglobin HbS.** Abnormal hydrophobic patch at the site of the 6-valine replacement is shown as projection in bottom left corner of HbS (1).

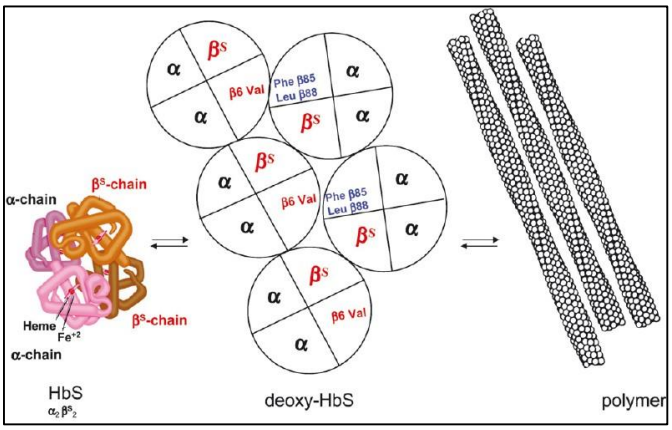

Figure 3. Polymerization of HbS. Deoxygenation of HbS causes a conformational change that allows interaction with other deoxygenated HbS hydrophobic regions, resulting in the formation of a 14 stranded helical fiber (2).

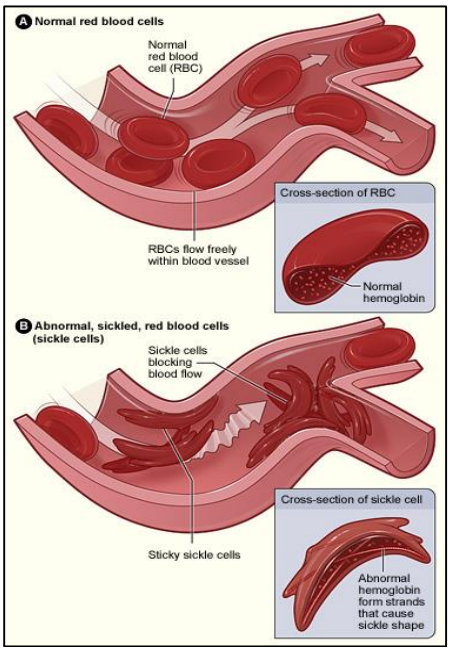

Figure 4. Sickle cell vasoocclusion. As deoxy HbS polymerizes and fibers align, the red cell is distorted into the rigid "sickle" shape, leading to vasoocclusion and other complications (3).

Phenotype	Clinical Syndrome
HbSS (SCA)	Severe or moderately severe
HbS/β^0 (Beta-Zero) Thalassemia	Severe or moderately severe (often indistinguishable from HbSS)
HbSC	Intermediate severity
Hb/β^+ (Beta-Plus) Thalassemia	Mild to moderately severe (variable in different ethnic groups)

Table 1. **SCD Phenotype and Clinical Severity.** The frequency and severity of clinical complications varies between SCD phenotypes. Symptoms are generally more severe in HbSS and HbS Beta-Zero Thalassemia and milder in HbSC and HbS Beta-Plus Thalassemia (4).

While the clinical course of SCD is remarkably unpredictable, the kidneys are especially sensitive to chronic sickling. This is not surprising, given the extremely high oxygen consumption by these organs and their innumerable small blood vessels. Though the kidneys make up less than 1% of total body mass, they receive approximately 25% of the total cardiac output (5). Furthermore, the renal medulla's naturally hypoxic, hyper-osmolar and acidic environment promotes RBC sickling within its network of microvasculature. A number of kidney disorders heralded by SCD, collectively referred to as sickle cell nephropathy (SCN), develop as a result of recurrent renal vassoocclusion, ischemia-reperfusion injury, and loss of nephron mass with compensatory glomerular hypertrophy. These renal disorders include hyposthenuria, hematuria, tubular acidification, hyperfiltration and proteinuria (6). Persistent injury from SCN can progress to Chronic Kidney Disease (CKD) and eventually End Stage Renal Disease (ESRD) (**Table 2**). A patient with ESRD cannot survive without dialysis or a kidney transplant.

Stage	Glomerular Filtration Rate (GFR) Parameters
Stage 1	Kidney damage with normal or increased GFR (≥ 90mL/min/1.73m^2)
Stage 2	Kidney damage with mildly decreased GFR (60-89 mL/min/1.73m^2)
Stage 3	Moderately decreased GFR (30-59 mL/min/1.73m^2)
Stage 4	Severely decreased GFR (15-29 mL/min/1.73m^2)
Stage 5	Kidney failure (ESRD); GFR < 15 mL/min/1.73m^2 or on dialysis

Table 2. Stages of Kidney Disease. CKD is defined as either kidney damage or a GFR <60 mL/min/1.73m^2 for equal to or greater than 3 months. Kidney damage is defined as pathologic abnormalities or markers of damage, including in blood or urine tests or imaging studies (7).

The earliest and most common renal complication in people with SCD is often hyposthenuria. Hyposthenuria describes the inability of the kidneys to concentrate urine when the kidneys' countercurrent exchange mechanism is interrupted by the loss of deep juxtamedullary nephrons due to vasoocclusion within the vasa recta; the long straight capillaries that extend into the medulla of the kidney and lie parallel to the Loop of Henle (**Figure 5)** (8). Hyposthenuria first becomes evident in early childhood, causing frequent urination and even nocturnal enuresis. A study of 213 individuals with SCA revealed that 42% of children from ages 6-8 and 9% of adults from ages 18-20 experienced involuntary voiding during sleep (10). Individuals with SCD and hyposthenuria are also at a higher risk for intravascular volume depletion, as they cannot properly respond to decreased oral fluid intake (8).

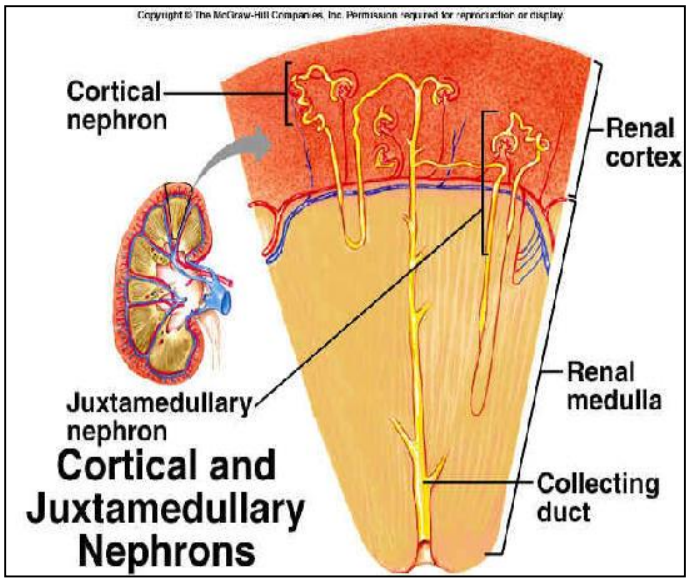

Figure 5: **Juxtamedullary Nephron.** Cross section of the kidney at the cortex and medulla border shows a normal juxtamedullary nephron that is damaged by vasoocclusion, leading to hyposthenuria (9).

Hematuria, or the presence of blood in the urine, is also a common manifestation of renal dysfunction in individuals with SCD. This condition is most often secondary to renal papillary necrosis caused by medullary infarction from obstruction of the vessels supplying the vasa recta. Sloughing of the renal papillae as a result of papillary necrosis can occasionally obstruct urine outflow, causing infection and, sometimes, acute renal failure (11). Excretion urography in individuals with SCD revealed a 23% prevalence of papillary necrosis and related hematuria in adult patients with SCA (12). SCD also commonly damages the distal tubule of the nephron, leading to hyperkalemia or an elevated concentration of the electrolyte potassium in the blood, as evidenced in various forms of renal tubular acidosis. Though the pathophysiologic mechanism is not completely understood, it is believed SCD renal damage causes the distal tubules to

become unresponsive to aldosterone. As a result, potassium excretion is inhibited and the pH of the blood is ultimately lowered (13).

While hyposthenuria, hematuria and renal tubular acidosis may arise from SCN, there is no evidence linking these disorders to progressive renal disease. They do not necessarily reflect decreased function in other areas of the kidney and cannot be considered early predictors of significant renal damage. On the other hand, the abnormal presence of albumin in the urine, or albuminuria, is widely considered to be the most accurate predictor of renal damage in individuals with SCD. Produced in the liver, albumin is one of the most abundant proteins in the blood. It is the first protein to leak into the urine when there is damage to the glomerulus, which normally functions as a filter, only allowing small positively charged waste molecules to pass from the blood into the urine (**Figure 6**). Microalbuminuria is defined by a urinary albumin excretion rate between 30 to 299 mg over 24 hours. With progressive renal damage, kidney function declines over time and the concentration of albumin in the urine increases. A urinary albumin excretion rate that is between 300 and 3,500 mg per 24 hours is called macroalbuminuria and is largely irreversible despite medical intervention (15-16). When there is enough damage to the glomeruli to cause macroalbuminuria, other proteins such as low molecular weight immunoglobins, lysozyme, insulin, and beta-2 microglobulin are often found in the urine as well (17). The abnormal level of any proteins in the urine, which may or may not include albumin, is referred to as proteinuria.

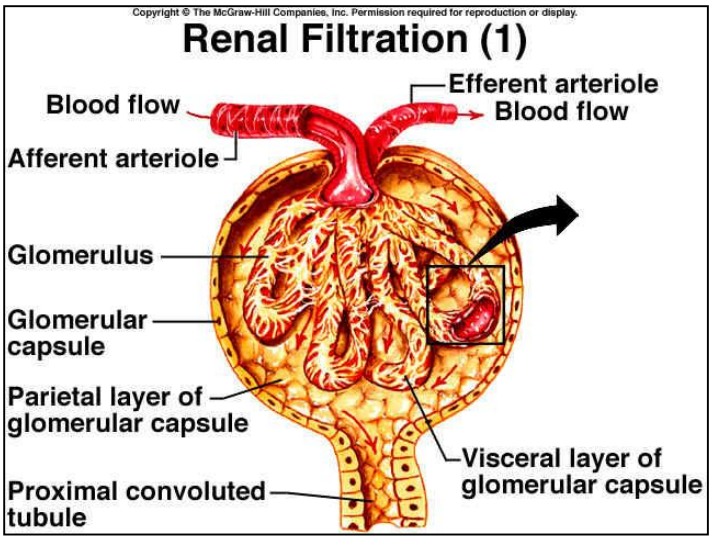

Figure 6. **Renal filtration.** Blood from the afferent arteriole is filtered in the glomerulus before returning to circulation via the efferent arteriole. When damaged, the glomerulus allows larger proteins in the blood to pass into Bowman's capsule, which is eventually excreted in urine (14).

The presence of protein in the urine of SCD patients is mediated initially by hyperfiltration, suggesting that the total renal blood flow (RBF), and consequently GFR, is increased from a young age in affected individuals. This is not the case in normal individuals, where a decrease in GFR is typically the first indication of sustained damage to the kidneys. Though the mechanisms behind this phenomenon are poorly understood, it has been suggested that RBF and GFR are initially increased in individuals with SCD as a result of the secretion of medullary vasodilator prostaglandins in response to the damage caused by increased renal hypoxia (18). Hyperfiltration leads to glomerular hypertension and hypertrophy, the sequelae of which is glomerulosclerosis, or scarring of the glomeruli. The abnormal anatomical changes brought on by this scarring result in functional abnormalities, namely a marked increase in glomerular permeability that leads

to microalbuminuria and progresses to macroalbuminuria and eventually proteinuria (6). Hyperfiltration begins to disappear as SCN progresses. In the prospective BABY HUG trial, GFR in infants with SCA was abnormally high, normalized into adulthood and declined further with age, suggesting that renal dysfunction in patients with SCA begins as early as infancy and progresses over time (19). Decreased GFRs is a common finding amongst SCD patients in their third or fourth decade of life. Unlike GFR, proteinuria increases in parallel with the progression of renal damage.

Detecting Microalbuminuria as a Screening Tool for CKD

While dipstick urinalysis (UA) is a common laboratory method used to screen for renal dysfunction, measuring microalbumin (MA) excretion rate by a specialized concentration assay is vastly preferred. Protein levels in the urine determined by UA are only semi-quantitative and cannot accurately measure the lower limits of microalbuminuria. MA excretion rates allow clinicians to detect renal dysfunction long before a positive protein result by UA or a decrease in GFR can be detected. Importantly, microalbuminuria from SCN can be detected in early childhood. Multiple studies in U.S. pediatric SCD have demonstrated a prevalence of microalbuminuria of 16-20% (20-22). The presence of albuminuria increases in parallel with age, as renal damage from SCD accumulates. A 2006 chart review of 300 adults with SCD revealed that 68% of patients with hemoglobin SS and 32% of patients with all other sickle genotypes had some amount of albumin in their urine (23). Similar results were reported in a 2010 investigation that explored the relationship between albuminuria and common laboratory

variables in individuals with SCD, where 33% of all adult subjects had microalbuminuria (24).

Albuminuria and proteinuria are strongly correlated with risk for future progression to CKD, which impacts 4 to 18% of all SCD patients (25). In a long-term study of individuals with HbSS, the development of CKD was closely associated with the presence of proteinuria and increased age. Of the 369 study subjects, 78 developed proteinuria. In the sub-population that developed proteinuria, 22% progressed to CKD and 7% advanced to ESRD requiring chronic dialysis (26). Similar results were achieved in a follow-up study of 38 patients with SCD, where significant proteinuria or azotemia occurred in 4-20% of subjects (27). Studies of non-sickle patient populations also support the findings that proteinuria predicts long-term development of CKD and ESRD (28).

By recognizing the beginning signs of SCN-induced CKD, early interventions can occur, resulting in better health outcomes and long-term savings in medical costs. The use of angiotensin-converting enzyme (ACE) inhibitors and angiotensin type II receptor blockers (ARBs) reduce the degree of albumin in the urine in patients with diabetic and non-diabetic nephropathy and thus slow or, in some cases, halt decline in renal function. An independent review of 11 randomized, controlled trials investigating the efficacy of ACE inhibitors for patients with nondiabetic kidney disease by Jafar et al. found that lowering albuminuria was associated with better renal outcome (29). In patients with type 2 diabetes and microalbuminuria, treatment with an ARB effectively prevented progression from micro- to macroalbuminuria (30). Falk et. al found that individuals with proteinuria treated with ACE inhibitors experienced a statistically significant reduction in

the degree of proteinuria and glomerular capillary hypertension (31). Hydroxyurea has also been shown to have a beneficial role in deterring renal damage in individuals with SCD, as it reduces sickling and thereby mitigates all organ damage. The prevalence of albuminuria among adult SCD patients at the University of Chapel Hill Kidney Center was lower among patients on hydroxyurea (34.7%) than those receiving no drug therapy (55.4%) (32).

Screening for SCN During Routine Health Care Evaluations

Over the past four decades, significant progress has been made in the treatment of SCD. The median life expectancy in the United States for individuals with SCA increased from less than 15 years in the 1970s to more than 40 years by the late 1990s (33). Today, many afflicted with the disease are even entering their sixth and seventh decades of life. The mortality rate in a cohort followed from 1999 through 2002 fell by 68% in SCD patients aged 0 through 3 years, 39% from age 4 through 9, and 24% from age 10 through 14 when compared to a cohort from 1983 through 1986 (34). This dramatic reduction in mortality can be attributed in part to the implementation of universal newborn screening, the introduction of prophylactic antibiotics and pneumococcal vaccinations, and parental education (35). Equally important, however, has been the growing emphasis on preventative medicine. Healthcare maintenance includes both the standard preventative care provided to all people and the specialized, interdisciplinary care that is unique to SCD and its multisystem clinical manifestations. One essential component of proper healthcare maintenance is the routine wellness examinations performed by hematologists

in large sickle cell centers. It is during these evaluations that providers regularly screen for complications of SCD, including renal dyfunction.

While routine healthcare maintenance is essential to the general health and wellbeing of all SCD patients, there is no "gold" standard of practice for patients with SCD. There are few evidence-based studies which could guide routine healthcare maintenance for SCD. In response to the absence of a universal standard of care, numerous sickle cell associations, comprised of a handful of multidisciplinary experts, have published general consensus guidelines and specific indicators of quality care. These guidelines reveal both subtle and significant variations across the different groups of sickle cell experts.

Within these guidelines, the topic of screening for renal function contained substantial inconsistencies, especially regarding the frequency, age limitations, and even the methods of detection (**Table 3**). Many of the groups defined age parameters vaguely. The New England Sickle Cell Consortium (NEPSCC) recommends renal screening in "older" children, while the University of South Alabama Comprehensive Sickle Cell Center does not indicate any age. While most groups advocate annual testing, the Sickle Cell Advisory Committee only ambiguously suggests "regular" UAs. In an effort to develop a universal set of quality care indicators in the management of SCD, Wang et al. did not consider routine screening for renal damage as an essential performance measure in healthcare maintenance (36-43).

Expert Panel	Recommendation
New England Pediatric Sickle Cell Consortium (NEPSCC)	Annually in "older" children
Expert Panel Report of the NIH 2013	Annually beginning at age 10
National Institute of Health: National Heart, Lung, and Blood Institute	Annually beginning at ≥ 12 months
Mid-Atlantic Sickle cell Disease Consortium (MASCC)	Annually beginning at birth
Sickle Cell Advisory Committee (SCAC)	"Regular" UAs as part of health maintenance visit, no beginning age indicated
Sickle Cell Disease Care Consortium (Texas Department of Health)	Annually beginning at 2 years old
University of South Alabama Comprehensive Sickle Cell Center	Annually, no beginning age indicated
Wang et al.	Screening for renal disease not considered a quality care indicator in routine health maintenance

Table 3: SCD expert group guidelines. Table above highlights the differences among the different sickle cell associations and their routine renal screen recommendations (36-43).

This study focuses specifically on the Sickle Cell Disease Program at Boston Children's Hospital (BCH), one of the largest in the northeast region. As a member of the NEPSCC, the program at BCH has adopted this consortium's routine healthcare maintenance guidelines. As mentioned above, the NEPSCC recommends annual renal function screening in "older children." Dr. Matthew Heeney, Director of the Sickle Cell Program at BCH and contributing member to the NEPSCC's published guidelines, defined "older children" as pediatric patients capable of providing urine specimens on demand and without assistance, or about five years of age.

Study Objectives

The primary objective of this thesis was to assess the practice of screening for renal disease at BCH's Sickle Cell Disease Program during routine healthcare maintenance evaluations. The findings of this study will have important clinical implications, as it aimed to answer the following questions:

- Does the institution follow the guidelines set forth by the NEPSCC?
- Do screening practices differ across certain patient demographics?
- Do screening practices differ across providers?
- How did screening by MA excretion rate compare to the frequency of UAs performed?

Secondary to the above objectives, this study hoped to encourage future dialogue and investigations that will address the following discussion points:

- How are providers educated in the practice of routine renal screening?
- What is the basis of practice (what are the physicians' reasoning for performing routine renal screenings)?
- Should a standard universal plan be instituted?

METHODS

This investigation was a retrospective chart review of BCH patients diagnosed with SCD.

Search Strategies

A list of all SCD patients seen at the BCH SCD clinic from the years 2011 through 2013 was generated by the administrative staff and maintained in a Microsoft Access database. The database contained names, demographics, and other identifying information for each patient. We then ran a query on Access to eliminate those patients who met the exclusion criteria and failed to meet the study inclusion criteria.

Study population data was obtained through PowerChart, the electronic medical record platform utilized by BCH. Study subjects' electronic medical records were accessed on an individual basis, drawing from the eligible patient list generated by Microsoft Access. Within PowerChart, data was obtained in hematology outpatient clinic notes and laboratory test results. Patients' lab results were filtered to include only urine tests performed during the calendar years of 2011-2013. A MA excretion rate and UA were considered part of the comprehensive clinical visit if the lab date directly coincided with a date on which a comprehensive sickle cell clinic note was created.

Patient laboratory results were accessed from PowerChart and cross-referenced with the dates of sickle cell clinic visits to determine how often UAs and MA excretion rates were ordered separately and in combination.

Study Population

Patients were included in the study if they met all of the following criteria:

- The patient was diagnosed with the sickle cell disease (HbSS, HbSC, HbS Beta-Plus Thalassemia, or HbS Beta-Zero Thalassemia)
- The patient attended a routine clinic visit at BCH's Comprehensive SCD Program at least once during the calendar years of 2011, 2012, or 2013
- The patient was at least 5 years old or older at the time of their first comprehensive clinic visit of the year

Patients were excluded from the study if they met any of the following criteria:

- The patient was diagnosed with Sickle Cell Trait (HbAS)
- The patient was under five years old at the time of a SCD clinic visit
- The patient was receiving chronic transfusion therapy[1]

Measures

Institutional Compliance With NEPSCC Guidelines

NEPSCC guidelines define a successful renal screen as the collection of a MA excretion rate, with or without a complete UA. All of the laboratory measurements on the urine specimens were performed at the clinical laboratory at BCH. The BCH clinical lab

[1] Patients receiving chronic transfusion therapy were excluded from analysis of institutional variability across treatment regimens. The department practice is to have routine comprehensive visits twice annually unless a patient is on a disease modifying therapy, in which case they are seen approximately every 3 months. Patients receiving chronic transfusion therapy, however, are often seen by a wider variety of providers and at locations outside of the hematology clinic, making it difficult to discern exactly when renal screens were due.

estimates MA excretion rate by measuring the urine albumin-to-creatinine (UACR) ratio. Spot, or random, UACR tests accurately predict the 24-hour MA excretion rate (44). UA orders were also tracked, but were not considered a renal screening event.

To determine whether or not the sickle cell program at BCH adhered to the NEPSCC guidelines, the frequency of successful renal screens performed within the study population was calculated. For each year from 2011 through 2013, every patient was determined to have either a successful renal screen or an unsuccessful renal screen. As most patients are seen at least twice annually, some patients had more than one MA excretion rate result within the same year. A single patient, however, could experience only one successful or unsuccessful event per year. Any additional MA results were not included in the compliance determination. The data for all three years was combined to determine the collective frequency of successful renal screens at BCH.

The overall frequency of UA's obtained within the entire study population was calculated in the manner described above.

Renal Screen Variability Across Patient Demographics

To determine variability in renal screening practices at BCH based on patient demographics, the study subjects were categorized into subpopulations based upon age, sex, sickle phenotype, and therapy. The overall frequency of successful renal screens for the subsets within each demographic category was determined by the same method described above in *Institutional Compliance With NEPSCC Guidelines*.

Variability in UA performance across patient demographics was determined in the same manner and compared to the frequency of MA orders.

Renal Screen Variability by BCH Provider

Study providers were defined as the hematology attending physicians responsible for the clinic visit. Interns, residents, fellows, nurse practitioners, and physician assistants who may have evaluated patients in clinic were excluded from the analysis of renal screening variability among providers.

To determine the variability in renal screening performance among providers, an inventory of the total number of sickle cell clinic visits was created for each individual provider. These clinic visits were classified as renal screen "due" and renal screen "not due." A renal screen was "due" if the patient had not yet had a MA excretion rate collected during a routine sickle cell visit for the year in question. A visit in which a renal screen was "not due" was defined as any visit that occurred after a renal screen was performed earlier in the same calendar year. Analysis of provider variability was determined by the portion of MAs obtained relative to MAs due.

Provider variability in UA orders was determined using the same method described above.

Statistical Analysis

Institutional Compliance

The Z-ratio between UA and MA frequency was computed using the VassarStats Computational Program (Poughkeepsie, NY) to find the significance of the difference between these two independent proportions at an alpha level of 5%. Using the VassarStats Computational program once again, the Z-ratio was defined for the proportion of MA and UAs collected separately. Those proportions were defined as: [(# of exclusive MAs performed) / (# of total MAs performed)] and [(# of exclusive UAs performed) / (# of total UAs performed)]. The total number of MAs performed = (exclusive MAs) + (MA performed in conjunction with UA). The total number of UAs performed was calculated in the same manner.

Variability Across Patient Demographics

Lower-Tailed or Higher-Tailed Hypothesis Tests were used with a 5% significance (or alpha) level and a Z or T cirtical value to compare the frequency of successful renal screens for each demographic subset to the overall institutional frequency, also referred to as the institutional standard.

We used the VassarStats Computational program to compare the significance of the difference between UA and MA orders across each patient subset.

RESULTS

Study Population

The subject selection screen yielded 330 patients who were eligible for analysis from 2011 through 2013. The analysis included 105 patients in 2011, 112 patients in 2012, and 113 patients in 2013. The demographics of the study population are represented in **Table 4**. The study population was evenly distributed by age group and sex**.** The HbSS sickle cell genotype accounted for a majority of the study population (84.8%). HbS Beta-Zero and HbS Beta-Plus were the only other sickle genotypes represented in the study. From 2011 through 2013, 56.4% of the total study population was being treated with hydroxyurea, 33% of the population received no disease-modifying therapy, and 11% were receiving chronic transfusion therapy.

Of the study population, 29.1 % had one comprehensive sickle cell clinic appointment per calendar year from 2011 through 2013 (n = 96). During the study period, 38.5% of the population had between 2 and 3 clinic visits per year (n = 127), while 32.4% visited the clinic 4 or more times per year (n = 107).

Institutional Compliance with NEPSCC Guidelines

Of the 330 patients, 113 (or 34.2%) had an annual MA excretion rate measured during a comprehensive sickle cell visit.

The frequency of UA's performed at BCH was not significantly different than the rate of MA excretion rates collected (32.1% vs. 34.2%, p = .281).

The majority of MAs and UAs were performed together (**Figure 7**). While BCH providers performed more MAs alone than they did UAs, there was no significant difference between the amount of MAs and UAs performed alone (39 vs. 26, p=0.084).

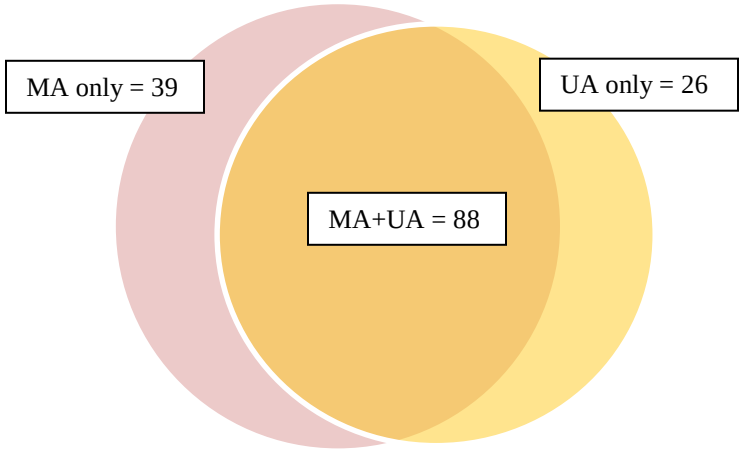

Figure 7. Comparison of MA excretion rates and UAs performed independently and in combination: 69% of all MA's were performed in combination with a UA. 77% of these UA's were performed in combination with a MA excretion rate.

Renal Screen Variability across Patient Demographics

Renal screen variability was assessed for each demographic category (**Table 4**).Compared to the institutional average (34.2%), the 5-9 year old group demonstrated a non-significant trend toward a lower frequency of successful renal screens during clinic visits. There was no statistically significant difference between the percentages of renal screens performed among the 10-14 year and 15 and older age groups and the institutional average. The percentage of MA excretion rates collected within the female

cohort was significantly higher than the institutional average (p = 0.024), whereas renal screens were performed significantly less often within the male population (p = 0.034) There was no significant difference between the frequency of renal screens among different sickle phenotypes or therapy cohort.

Age Group	% of Total Population	% MA performed at least once	p-value
5-9	105/330 = 31.8%	30/105 = 28.6%	0.111
10-14	108/330 = 32.7%	40/108 = 37%	0.271
15+	117/330 = 35.5%	43/117 = 36.8%	0.278
Sex			
Female	156/330 = 47.3%	65/156 = 41.7%	**0.024**
Male	174/330 = 52.7%	48/174 = 27.6%	**0.034**
Phenotype			
HbSS	280/330 = 84.8%	96/280 = 34.3%	0.486
HbS Beta-Zero	29/330 = 8.8%	7/29 = 24.1%	0.126
HbS Beta-Plus	21/330 = 6.4%	10/21 = 47.6%	0.097
Therapy			
Hydroxyurea	186/330 = 56.4%	69/186 = 37.1%	0.202
None	109/330 = 33.0%	40/109 = 36.7%	0.293

Table 4. Renal screen variability by patient demographics. Sex was the only patient variable category to show a statistically significant difference in renal screen performance compared to the institutional standard. Other variables, such as age and genotype showed pattern of differences, but were not large enough to be considered statistically significant.

UA vs. MA in Variability Across Patient Demographics

The frequency of UAs performed within each patient population subset was similar to the frequency of MAs performed within the same demographic category. We found no statistically significant difference within any population subset when comparing UA to MA renal screens (**Table 5**).

Age Group	% UA performed at least once	p-value (compared to % MA performed)
5-9	35/105 = 33.3%	0.228
10-14	36/108 = 33.3%	0.284
15+	35/117 = 29.9%	0.134
Sex		
Female	60/156 = 38.5%	0.282
Male	46/174 = 26.4%	0.405
Phenotype		
HbSS	90/280 = 32.1%	0.295
HbS Beta-Zero	5/29 = 17.2%	0.259
HbS Beta-Plus	11/21 = 52.4%	0.379
Therapy		
Hydroxyurea	63/186 = 33.9.1%	0.258
None	39/109 = 35.87%	0.444

Table 5. UA vs. MA performance across patient demographics. UAs were performed in near identical frequency to MAs across each patient demographic category.

Renal Screen Variability among BCH Providers

During the study period, 28 different BCH providers performed a total of 886 comprehensive sickle cell evaluations on the collective study population. Provider P-10 completed 549 (62%) of these examinations. Using the Extreme Studentized Deviate (ESD) test, we determined that this physician was a statistical outlier, and did not utilize this data in the analysis of renal screening variability among BCH providers.

For the 27 remaining providers, renal screens were collectively considered "due" in 281 of the 337 sickle cell clinic evaluations. The frequency of obtaining a "due" renal screen varied significantly by provider (**Figure 8**).

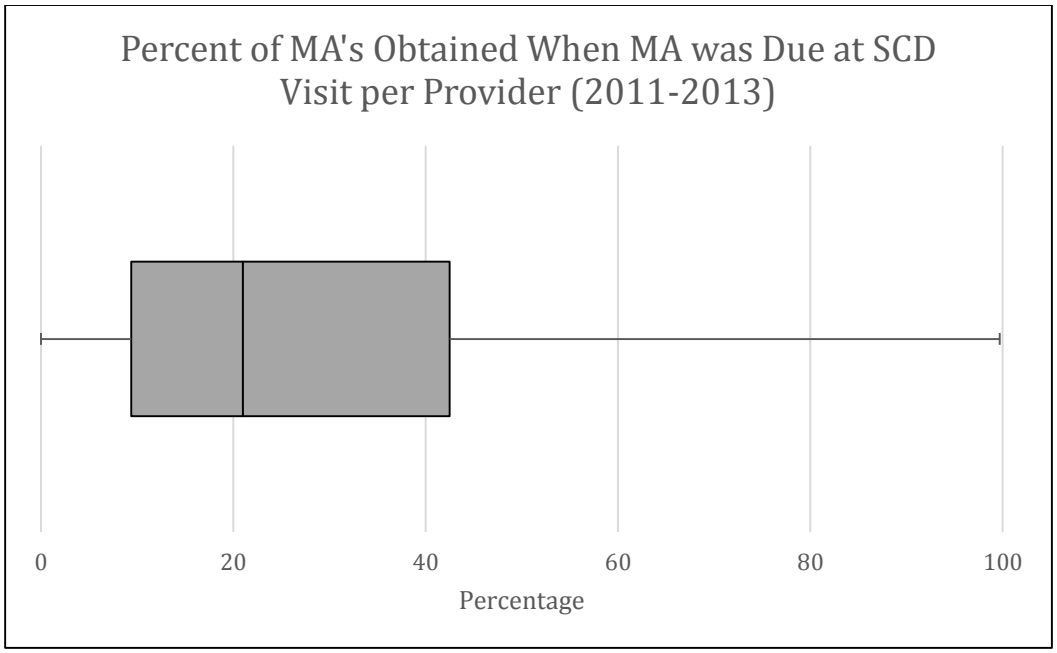

Figure 8. Provider variability in performing renal screens at SCD visits. Half of the total providers in the study performed a renal screen when it was "due" at a SCD clinic visit between 9.4% and 42.5% of the time.

There was significant variation in the number of routine sickle cell visits across providers (**Figure 9**). Provider P-06 had the most visits "due" for a renal screen (n = 56), while providers P-14 and P-20 both had the least number of visits "due" (n = 1). There was a general tendency across all providers not to collect urine specimens for MA excretion measurement in the majority of visits that were "due" for renal screens. The average number of clinic visits with a renal screen due was 10.4 per provider, while the providers collectively averaged 2.15 successful renal screens.

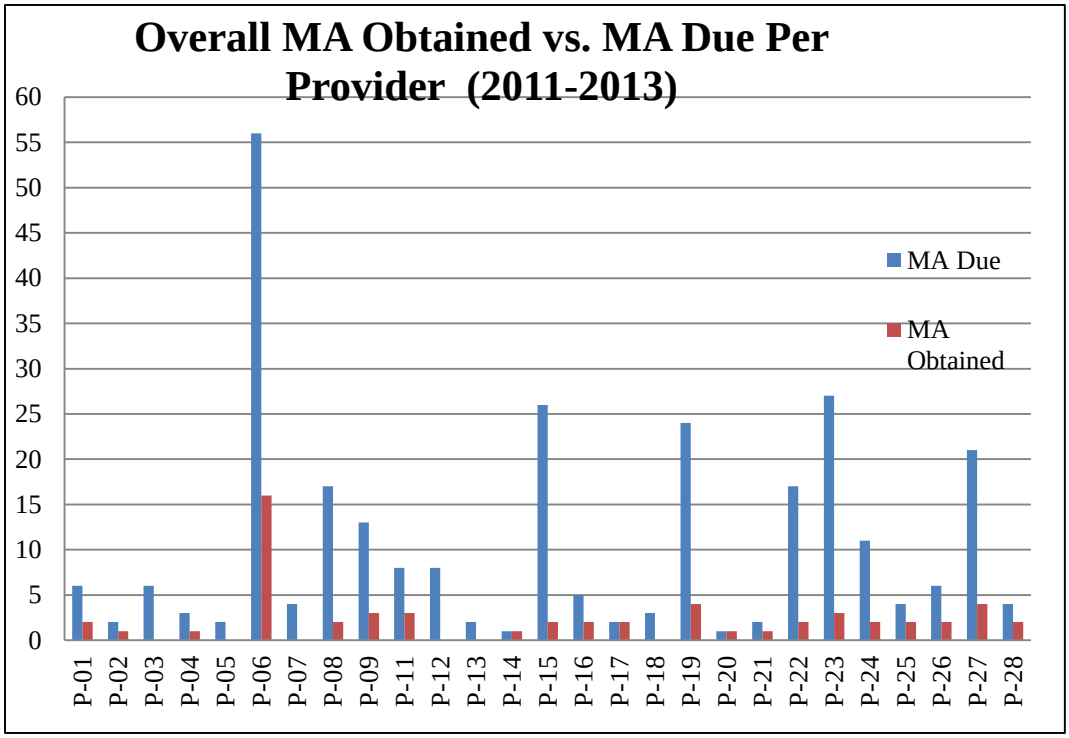

Figure 9. MA excretion rates performed by provider. Each provider experienced a significant difference in the number of SCD clinic visits considered "due" for a renal screen. In general, providers failed to collect renal screens in a majority of these visits.

UA vs. MA in Provider Variability

In general, individual providers successfully performed UAs at the relative same frequency as MAs. Only provider P-10 showed a significant difference (16 MAs vs. 5 UAs). While still significant, there was less variability across providers in the performance of UAs compared to the performance of MAs. The providers collectively averaged 1.85 successful UA collections each (**Figure 10**).

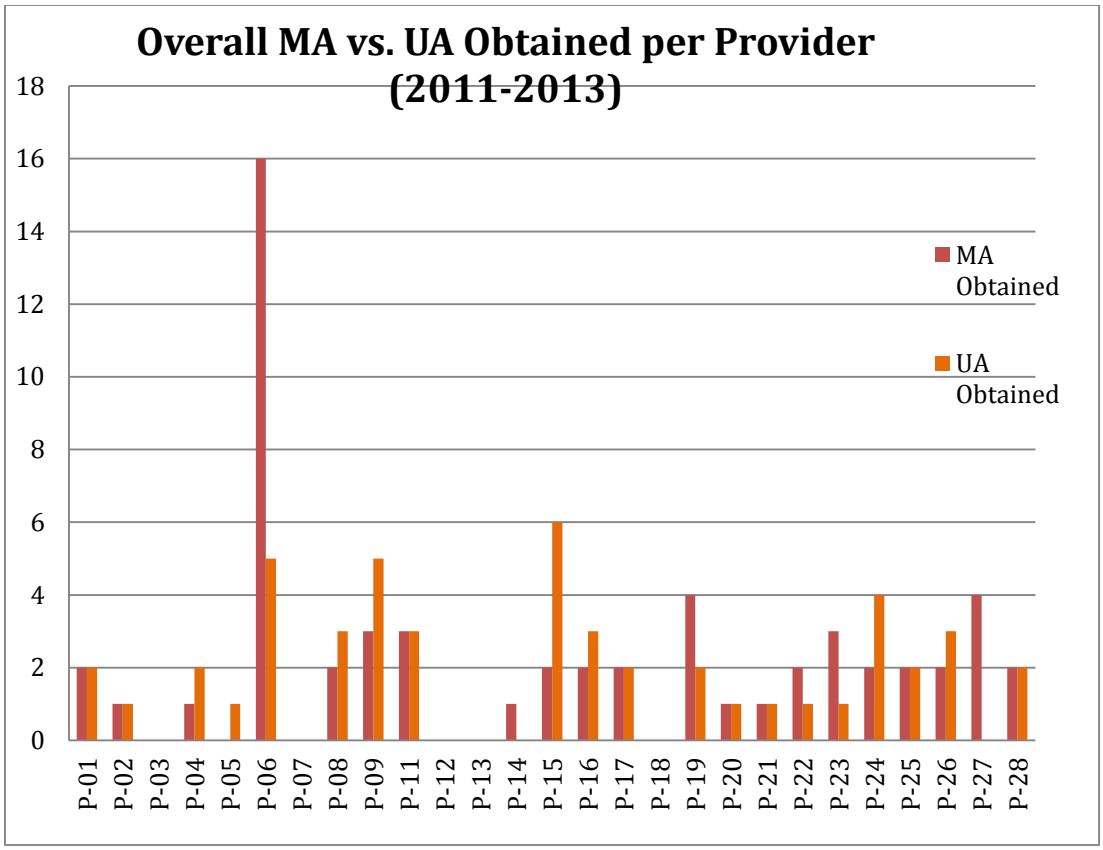

Figure 10. UA performance compared to MA performance by provider. With the exception of Provider P-06, providers tended to perform UAs at a similar frequency as MAs. There was significant variability from one provider to another in the performance of UAs, though it was less than the variability across MAs.

DISCUSSION

The aim of this study was to assess the practice of screening for renal function at BCH's SCD Program during routine healthcare maintenance evaluations. As a department, BCH providers successfully obtained a renal function screening test in 34% of cases. BCH providers are more likely to order renal screens for female patients than male. Better designed studies might be necessary to more accurately assess if other patient variables, such as sickle phenotype, also influence the frequency of renal screens performed at BCH. The frequency of routine renal screens performed at the sickle cell clinic varies significantly from one provider to another. Finally, UAs are performed at a similar frequency as MA excretion rates. Although most UAs are collected in combination with MA excretion rates, a surprising number of UAs are collected alone.

While prior studies have emphasized the strong correlation between SCD and proteinuria, and its frequent progression to CKD (20-27), specific studies examining the process of screening for renal failure by MA detection in SCD patients have been lacking. Renal damage is a common and serious complication in SCD. The long-term, multi-center Cooperative Study of Sickle Cell Disease (CSSCD) identified renal failure as the major risk factor for early mortality in adult patients with SCD (33). Intervention with ACE inhibitors, ARBs, and perhaps even hydroxyurea can reduce proteinuria and impede the progression of renal damage. Early detection of kidney damage by routine renal screens, therefore, has great clinical potential.

The first objective of this study was to evaluate if the SCD Program at BCH adhered to the NEPSCC guidelines. The NEPSCC guidelines suggested an annual renal screen in children at least five years of age. While the BCH department fell short of that goal, there are several factors which may have complicated our analysis. First, patient compliance with physician orders may have played a complicating factor. At BCH, patients visit the outpatient laboratory for blood and urine specimen collection before or after their routine SCD clinic visit. Through chart review alone, it is impossible to distinguish between renal screens not performed because of poor patient compliance and renal screens not performed because of a provider's failure to order or collect one. Secondly, pediatric patients are sometimes simply not able to void urine on demand. The difference between ordered renal screens at BCH and the recommendation by the NEPSCC may not be as large as the data suggests for completed screens.

The second objective of the study was to determine if the performance of renal screens was influenced by certain patient demographics, specifically age, sex, sickle phenotype, and disease-modifying therapy. While the youngest age group (5-9 years old) tended to have a lower frequency of renal screens, this finding was not particularly surprising given that renal that renal abnormalities due to SCN become more common with increasing age (45-46). It is possible, therefore, that some providers are less likely to order renal screens for younger patients.

Interestingly, the study found significant differences between the frequencies of renal screens performed within the male and female populations. The data suggests females are far more likely to have a renal screen performed during their routine clinic

evaluations than their male counterparts. This result is particularly surprising, as there is no proven or even perceived correlation between sex and the development of CKD (47-49). It is possible, then, that this gender bias is predicated on clinical indications that are outside the scope of CKD and SCD, such as the role of gender in childhood intellectual and emotional development. Apart from a study that investigates BCH providers' basis of practice, it would be useful to determine if this gender bias permeates across other sickle cell centers, or if it is exclusive to BCH.

While there were no statistically significant differences between the institutional average and the renal screen frequency within the three sickle phenotype subsets, the data does reveal some interesting variability. Patients with the sickle phenotype HbS Beta-Zero tended to have less renal screens performed, and patients with the sickle phenotype HbS Beta-Plus tended to have more renal screens performed. Importantly, the populations in the HbS Beta-Zero and HbS Beta-Plus subsets were significantly smaller than the HbSS subset. The limited sample size in these particular cohorts likely skewed the data. Future studies may benefit from repeating this particular part of the investigation with a greater population of patients with the HbS Beta-Plus and HbS Beta-Zero phenotypes.

The third objective of this study was to assess renal screen variability across BCH providers. The study found significant variability in the frequency with which renal screens are performed among providers. The validity of these findings, however, is limited by the small sample size of sickle cell visits for many of the attending physicians. Nearly half of the providers (13 of the 27) only oversaw 5 or less clinic visits that were

"due" for a renal screen during the entire three-year study period. A study with more visits per provider or in which all providers saw the same number of SCD patients due for a renal screen would produce a more accurate assessment of provider variability.

Interestingly, there was no significant difference between the frequency of MA and UA collection. Unlike MA excretion rates, UAs can help detect a number of disorders not necessarily related to proteinuria and CKD, such as diabetes, bladder infections and kidney stones (50). They are also fast and inexpensive to obtain and, perhaps most importantly, can be performed on the same urine specimen used to find MA excretion rates. This might explain why UA's and MA excretion rates were obtained jointly in the majority of clinic visits where at least one test was performed. On the other hand, the data reveals a higher than expected frequency of UAs obtained in the absence of a MA excretion rate. UAs are far less accurate in detecting proteinuria and is a clinically inferior screening method compared to the measurement of MA excretion rate. Future investigations should further explore provider knowledge and beliefs.

Future Research

While this study describes the frequency of routine renal screens performed for SCD patients at BCH and its many affecting factors, it does little to elucidate the exact reasons behind why certain tests to detect renal dysfunction were performed at some visits and for some patients, but not for others. It would be of future interest, then, to develop a study that aims to profile providers' beliefs, awareness of clinical guidelines,

and overall knowledge in order to provide insight into the influence of their decision making.

Furthermore, this study can serve as a useful framework to guide future efforts to improve clinical practice. Further investigations should be conducted following interventions designed to increase routine renal screen performance at the sickle cell clinic. Such interventions might include provider education and the development of a laboratory order template for sickle cell clinic visits that includes a renal screen by microalbumin excretion rate.

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CURRICULUM VITAE