Opportunities to Improve Transcranial Doppler Screening Among Children with Sickle Cell Disease

by

Sarah Erin Leasure Reeves

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Doctoral Committee:

Associate Professor Lynda D. Lisabeth, Chair
Associate Professor Matthew L. Boulton
Professor Thomas M. Braun
Research Associate Professor Kevin J. Dombkowski
Professor Heather J. Fullerton, University of California, San Francisco

Dedication

For my grandma. She would be the proudest of all.

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List of Abbreviations

AAN	American Academy of Neurology
AAP	American Academy of Pediatrics
ACS	American Community Survey
AHA	American Heart Association
AMA	American Medical Association
CI	Confidence Interval
CPT	Current Procedural Terminology
ED	Emergency Department
GEE	Generalized Estimating Equations
Hb	Hemoglobin
ICA	Internal Carotid Artery
ICD-9	International Classification of Diseases, Ninth Revision
IQR	Interquartile Range
MCA	Middle Cerebral Artery
MDCH	Michigan Department of Community Health
NBS	Newborn Screening
NHLBI	National Heart Lung and Blood Institute
NPI	National Provider Index
OR	Odds Ratio
PCP	Primary Care Physician
QIC	Quasi-Akaike Information Criterion
SCD	Sickle Cell Disease
SCDAA	Sickle Cell Disease Association of America
SD	Standard Deviation
STOP	Stroke Prevention in Sickle Cell Anemia
TCD	Transcranial Doppler Screening

Abstract

Children with sickle cell disease (SCD) are at an increased risk of stroke. Transcranial Doppler (TCD) screening assesses the risk of stroke in children with SCD by measuring blood velocity in cerebral vessels. High velocities are strongly associated with stroke risk and indicate the need to begin chronic blood transfusions as a stroke prevention strategy. Although chronic blood transfusions have been known to reduce stroke risk by up to 92% since the nineties, rates of TCD screening remain low and few factors have been identified that are associated with receipt of TCD screening. This dissertation investigated factors that may influence receipt of TCD screening among children with SCD on multiple levels by 1) assessing TCD screening rates and frequency and predictors of missed opportunities among children with SCD in Michigan Medicaid, 2) exploring the role of neighborhood factors in receipt of TCD screening among children with SCD in Michigan Medicaid residing in Wayne County, and 3) investigating physician awareness, attitudes and knowledge of TCD screening guidelines, along with physician perceived barriers to screening.

Assessment of TCD screening rates and missed opportunities in children with SCD enrolled in Michigan Medicaid showed that TCD screening rates were low, particularly among adolescents. Low TCD rates coupled with high healthcare utilization resulted in frequent missed opportunities for TCD screening. Increasing age was associated with an increased likelihood for a missed opportunity, while more than 4 outpatient visits and previous receipt of TCD screening decreased the odds for a missed opportunity. No association was found between receipt of TCD screening and

socio-demographic characteristics of the child's neighborhood, nor was any spatial pattern of screening rates discovered across neighborhoods. Although physicians believed that children with SCD should receive TCD, significant differences existed in awareness, attitudes and knowledge of TCD screening guidelines across specialties, and knowledge of specific TCD recommendations was low for all physicians. The culmination of this work suggests that future studies and interventions are necessary to continue to identify and intervene on factors associated with TCD screening among children with SCD to avert the consequences of stroke in this high-risk population.

Chapter 1

Introduction

1.1 Introduction

Pediatric stroke is a leading cause of childhood death. Among survivors, pediatric stroke is associated with significant morbidity such as stroke recurrence and cognitive and behavioral deficits. In the US, annual pediatric stroke incidence is ~2.4 in 100,000; however, risk in children with sickle cell disease (SCD) is much higher. Without intervention, ~10% of children with SCD will have a stroke by age 20. These strokes are largely preventable. Transcranial Doppler (TCD) screening is used to detect high blood flow velocities in cerebral vessels of children. High velocities indicate an increased stroke risk and the need to begin stroke prevention in the form of blood transfusions with the goal to reduce hemoglobin S below 30%. Once transfusions are initiated, stroke incidence is reduced by up to 90%. Given the importance of stroke prevention in this population, the National Heart Lung and Blood Institute (NHLBI) recommends children with SCD receive one TCD screening per year from ages 2 to 16 years. However, rates of screening remain low, even in comprehensive sickle cell centers. Little is known regarding the factors that influence TCD screening among children with SCD to inform interventions to improve screening in this high-risk population.

The objective of this dissertation was to identify policy and practice intervention targets to improve access to and use of TCD screening with the intent to reduce pediatric stroke among children with SCD. The research used Michigan Medicaid data from 2007 to 2011 to identify rates of TCD screening in Michigan, along with the

frequency and individual-level correlates of missed opportunities for TCD screening. The role of neighborhoods in the receipt of TCD screening was also investigated. In addition, provider knowledge regarding current recommendations for TCD screening and provider perceived barriers to TCD screening among children with SCD were explored.

1.2 Specific Aims and Hypotheses

The specific aims and hypotheses for this dissertation were as follows:

Aim 1a: Determine the frequencies of TCD screening and missed opportunities for TCD screening among children with SCD continuously enrolled in Michigan Medicaid for at least one year from 2007 to 2011.

Hypothesis 1a: Rates of TCD screening will be low and the frequency of missed opportunities for TCD screening will be high, suggesting significant potential to increase TCD screening rates through reduction of missed opportunities.

Aim 1b. Identify individual-level correlates (SCD-related healthcare utilization, SCD comorbidities, and previous receipt of TCD screening, demographics and sickle cell type) of missed opportunities among children with SCD continuously enrolled in Michigan Medicaid for at least two years from 2007 to 2011.

Hypothesis 1b: SCD-related emergency department utilization, hematologist visits, SCD comorbidities, sickle cell type (Hemoglobin SS), SCD severity, decreasing age and female sex will be associated with fewer missed opportunities.

Aim 2a: Investigate the spatial pattern of TCD screening rates across neighborhoods of children with SCD continuously enrolled for at least one year in Michigan Medicaid from 2007 to 2011.

Hypothesis 2a. A spatial pattern of TCD screening rates will be present across neighborhoods and pockets of neighborhoods with low TCD screening rates will be identified.

Aim 2b. Identify neighborhood-level factors related to the receipt of TCD screening among children with SCD continuously enrolled in Michigan Medicaid for at least one year from 2007 to 2011.

Hypothesis 2b. Increasing neighborhood disadvantage, as measured by percent less than high school education, percent African American residents, percent unemployment and decreasing median household income, will be associated with lack of receipt of TCD screening among children with SCD.

Aim 3: Explore factors that may be related to adherence to TCD screening guidelines among physicians (awareness, attitudes and knowledge of guidelines) and assess physician-perceived barriers to TCD screening among pediatric primary care physicians of children with SCD in Michigan and pediatric hematologists and neurologists across the United States.

Hypothesis 3a: Awareness, attitudes and knowledge of TCD screening guidelines will differ by provider specialty.

Hypothesis 3b: Physician perceived barriers to TCD screening in children with SCD will be identified.

A more complete understanding of the determinants of TCD screening among children with SCD is integral in order to develop targeted interventions to increase TCD screening rates. The results of this research could inform interventions at multiple levels (individual, area, provider) aimed at improving TCD screening in this high-risk population.

1.3 Background

Public Health Importance of Pediatric Stroke

Incidence rates for pediatric stroke are estimated to range from 1.3-13.0 per 100,000.[1,2] Pediatric stroke is associated with significant mortality, morbidity and cost. Mortality rates from pediatric stroke are 0.23 per 100,000,[3] and pediatric stroke is one of the top ten causes of childhood death in the US.[4] In one study of children hospitalized with stroke, 74% showed significant neurological deficits at discharge.[5] Another study focusing on the one year post-stroke period showed 54% of children with severe neurological impairment.[6] Health related quality of life is significantly lower among children who have had a stroke compared to their healthier counterparts.[6] Rates of recurrence are high, with 25% of children having a recurrent stroke within two years of initial stroke.[7] The median five year direct costs of inpatient and outpatient care of a pediatric stroke patient total $135,161, with the initial hospital admission contributing $81,869.[8] The lifelong cost of pediatric stroke is likely far greater due to the large burden pediatric stroke places on both families and society.[9]

Risk factors for pediatric stroke differ from those for adult stroke. Identified risk factors for arterial ischemic stroke include sickle cell disease (SCD), varicella infection,

arteriopathy and cardiac disease. These risk factors vary by both child age and geographic location.[10] Vascular abnormalities are commonly associated with pediatric hemorrhagic stroke.[11]

Disparities in pediatric stroke exist as African American children are at a twofold greater risk of stroke compared to white children; however, the disparities between black and white children have decreased over the past decade for ischemic stroke but remained stable for hemorrhagic stroke.[12,13] This disparity may be largely due to SCD which occurs primarily in African Americans. The reduction in this disparity over time may be partially attributable to the impact of stroke prevention efforts among children with SCD. Males compared with females are at an increased risk of both incident stroke and death due to pediatric stroke across all ages and stroke subtypes.[12,14]

Sickle Cell Disease

Sickle cell anemia is a genetic condition due to a point mutation in a hemoglobin molecule. Sickle cell hemoglobin (HbS) is a recessive trait that can be inherited as sickle cell trait (one HbS gene) or SCD.[15] There are three main subtypes of SCD: HbSS (two sickle cell genes), HbSC (one sickle cell gene and one gene for abnormal hemoglobin called C) and HbS β-thalassemia (one sickle cell gene and one β-thalassemia gene, a type of anemia).[16] SCD currently affects approximately 70,000-100,000 Americans. SCD disproportionately impacts minorities; 1 out of 500 African American births and 1 out of 36,000 Hispanic American births are diagnosed with SCD.[16,17] Sickle cell trait is generally asymptomatic but a genetically important variant which affects 1 in 12 African American births.

In individuals with SCD, hemoglobin has a sickle shape as opposed to the disc shape in individuals with normal hemoglobin. This sickle shape has two major health consequences: anemia and blood vessel occlusion. The sickle shape of the cells promotes adherence to the endothelial cells which leads to endothelial activation. Endothelial activation initiates the release of several activator substances, along with impairing the release of nitrous oxide (a vasodilator). These factors cause the blood vessel occlusion in SCD.[15] The severity of symptoms in SCD is controlled by the amount of sickling of the HbS, along with other factors such as temperature, stress, infection, dehydration, or hypoxia. Blood vessel occlusion can result in severe pain crises in individuals with SCD, which can happen suddenly and in many areas of the body. Acute chest syndrome (atypical pneumonia), growth retardation, osteomyelitis, swelling, neurological complications and splenic injury are common morbidities of SCD.[15] Additionally, children with SCD have a significant increased risk for infection as they are 100 times more likely to develop pneumococcal infection than children without SCD.[18] The high rate of health complications among children with SCD also leads to increased healthcare utilization and expenses. Children with SCD are 7-30 times more likely to be hospitalized, 2-6 times more likely to visit the emergency department, and have over 8 times the healthcare expenditures than their healthier counterparts.[19-21]

To facilitate early identification of children with SCD, all states perform Newborn Screening (NBS) upon birth.[22] The American Academy of Pediatrics (AAP) has released recommendations regarding coordination between NBS and primary care physicians (PCPs) in the reporting of NBS results, and states are also responsible for program-specific information regarding follow-up.[23] Despite identification of SCD at birth, delayed

or inadequate preventive services may lead to serious complications and/or premature death in children with SCD.[18,24,25]

Pediatric Stroke and Sickle Cell Disease

The sickle shape of the blood cells among those with SCD prevents smooth motion through blood vessels. These cells can easily form clumps that may then get stuck in the blood vessels. This clumping of blood vessels may explain small vessel infarcts. There is no known association between sickle cell trait and stroke;[26] however, children with SCD have over three hundred times the stroke risk than children without SCD or heart disease.[27] Without intervention, approximately 11% of children with SCD will have a stroke by age 20[27,28] and 24% by age 45.[28,29] The mechanism for stroke in patients with SCD is poorly understood.

Predicting Stroke Risk Among Children with SCD

Transcranial Doppler Ultrasonography (TCD) has been shown to have 90% sensitivity and 100% specificity in detecting significant intracranial lesions by detecting high blood flow velocities in arteries, specifically the distal internal carotid artery (ICA) or proximal middle cerebral artery (MCA).[30,31] Children over the age of two with a time-average mean maximum blood flow velocity of 200cm/sec or greater as measured by TCD have been shown to have 27 times the risk of stroke than children with velocities less than 200cm/sec. This corresponds to a 40% risk of stroke among those with high velocities within 3 years.[30] TCD screening is a reasonable method to assess stroke risk among children with SCD, as it is safe, non-invasive and low cost.[32] Although other predictors of stroke have been examined such as hematocrit levels and white blood cell count, TCD has been shown to be the only independent predictor of stroke.[31]

Stroke Prevention Among Children with SCD

The Stroke Prevention in Sickle Cell Anemia (STOP) trial aimed to test the hypothesis that blood transfusions would reduce the risk of stroke among children with SCD. Children with SCD with no history of stroke, no transfusion contraindications, and at no additional risk of stroke due to external factors received TCD screening. Results from the TCD screening were characterized as normal (blood velocities in the MCA or ICA less than 170cm/sec), conditional (velocities 170-200cm/sec) or abnormal (velocities 200cm/sec or greater). Children with at least two abnormal TCD results were randomized to either receive standard care for children with SCD (vaccinations, folic acid supplementations, etc.) or transfusions every 3-4 weeks with the goal to reduce hemoglobin S concentration to below 30% of total hemoglobin. The primary endpoint of the trial was stroke as determined by a blinded physician panel. A total of 130 children were enrolled and 63 were randomized to receive transfusions. Eleven children in standard care and one child on transfusions had a stroke, resulting in a 92% stroke relative reduction among children receiving transfusions as opposed to standard care.[24] The trial was stopped early due to the large benefit of transfusions. Given the results of the STOP trial, the NHLBI released a clinical alert in 1997 recommending TCD screening for children with SCD between the ages of 2 to 16 years.[33]

The STOP2 trial randomized children who had received exchange transfusions for thirty months or longer to either continue or discontinue exchange transfusions. Discontinuation led to a high rate of abnormal blood flow velocities on TCD screening and an increased risk of stroke.[34] Once again, the trial was stopped early due to the benefit of continued exchange transfusions.

Another potential method of stroke prevention that has received recent attention is hydroxyurea therapy. Hydroxyurea, a medication used for pain treatment in adults with SCD, has been shown to reduce blood velocities as detected by TCD screening in children with SCD;[35] however, a recent study investigating if hydroxyurea was as effective at preventing recurring strokes in children with SCD was halted as the hydroxyurea approach seemed no better than the standard treatment of exchange transfusions.[36]

Recommendations for TCD Screening

Given the importance of TCD screening to indicate the need to begin stroke prevention efforts, numerous organizations have released guidelines regarding TCD screening among children with SCD. These guidelines differ among the organizations in integral areas. NHLBI guidelines, "Management of Sickle Cell Disease" (2002), recommend TCD screening to start in children with SCD (HbSS) at age two and continue until age sixteen. If TCD screening is normal (blood velocity <200 cm/second), children are recommended to receive one screening annually. If TCD screening results are >200 cm/second, the results are considered abnormal. Abnormal results indicate the need for additional screening.[25] Recommendations from the American Heart Association (AHA) are similar but less specific, indicating that children with SCD in general should be screened with TCD beginning at two years of age, and screened more frequently if velocities are near the 200 cm/sec cutoff.[37] The AHA also suggests using peak systolic velocities as a measurement as opposed to time-averaged means of maximum velocity used in the STOP trial. The American Academy of Neurology (AAN) recommends beginning TCD screening at two years[38] and the AAP recommends

physicians discuss TCD screening if available from ages one to thirteen; however, provides neither specific indications for the timeliness nor appropriateness of TCD screening.[39]

The AAP recommendation has received backlash from physicians, prompting a letter to the editor questioning the weak recommendations in the face of compelling evidence.[40] The AAP reply to the letter defends the organization's position, stating that the long-term risks and benefits are unclear for TCD screening due to transfusion related morbidity and lack of standardization of screening methods. The significant ambiguities and disparities that exist between multiple national organizations' guidelines (Table 1.1) may lead to differences among physicians in recommendations regarding TCD screening.

Rates of TCD Screening Among Children with SCD

Although rates of TCD screening have increased six-fold since the STOP trial among children with SCD, they remain significantly lower than the NHLBI guidelines of one TCD screening per year in numerous settings.[41-43] The TCD screening rate in a large healthcare plan was 11.4 per 100 person-years in 2004.[41] At a large, comprehensive sickle cell center in Philadelphia, 84% of 530 children with SCD at the center received screening over an eight year period, averaging only 3.3 screenings per child.[44] At the Texas Children's Sickle Cell Center, the average yearly screening rate for eligible patients was 45%.[42]

A recent study utilized administrative claims from Tennessee Medicaid and chart review in two sickle cell centers to show that 68.6% of children with SCD received at least 1 TCD screening within a 12 year period, and yearly cumulative incidence rates of

annual TCD screening increased from 2.5% to 68.3% from 1997-2008.[45] To date, TCD screening rates have largely been explored at comprehensive SCD care centers, which may not be representative of screening rates in the broader population of SCD patients.

Individual-Level Predictors of TCD Screening Among Children with SCD

Predictors of TCD screening are not well understood. Sickle cell type HbSS, distance of less than 30 miles to a vascular laboratory, and presence of hypertension have been shown to be predictors of TCD screening in a California HMO. [41] At two sickle cell clinics in Tennessee, calendar year, maternal education, and increased number of sickle cell related outpatient visits were associated with increased screening rate.[45] Aside from these few studies, there is little published data on the factors associated with TCD screening. Additionally, these factors have been explored in specific SCD populations; therefore, these associations may not be generalizable to the population of children with SCD as a whole.

Barriers to TCD Screening Among Children with SCD

Both caregivers and providers play an integral role in stroke prevention among children with SCD. A survey of caregivers of children with SCD indicated lack of knowledge as the most important barrier to annual TCD screening, with over one-fifth of caregivers unaware of TCD screening.[46] A lack of self-efficacy such as believing there is nothing one can do to prevent stroke was another barrier identified among caregiver respondents. Importantly, the vast majority of caregivers expected their healthcare team to recommend yearly TCD screening and did not initiate a request for TCD without this recommendation.[46]

Little is known regarding provider knowledge and perspectives regarding TCD screening among children with SCD. A survey of hematologists in the United States pointed to poor patient adherence, distance to a vascular laboratory, and lack of appropriate staff to perform and interpret TCD screening results as perceived obstacles to TCD screening.[47] The generalizability of this study is limited by both a low response rate and inclusion of hematologists only. The AAP recommends each child with SCD have a "medical home," which may be either a sickle cell center or a primary care physician giving day-to-day care to the patient with referrals to specialists for the treatment of severe complications.[39] Therefore, it is important to understand the attitudes and practices of pediatricians treating children with SCD. A national random sample of pediatricians showed only 35% of the pediatricians would be comfortable being the primary care physician for a child with SCD.[48] One study showed that a majority of pediatricians are familiar with guidelines regarding antibiotic prophylaxis among children with SCD;[49] however, TCD guidelines are newer and more controversial than guidelines regarding antibiotic prophylaxis. No study to date has investigated pediatricians' knowledge regarding TCD screening or their perceived barriers to TCD screening among children with SCD.

Missed Opportunities and Strategies to Improve TCD Screening

Healthcare utilization is significantly higher in children with SCD than in children without SCD, although the type of healthcare can vary substantially between ED visits, hospitalizations, outpatient visits, home healthcare visits and participation in comprehensive SCD healthcare.[50] With high healthcare utilization among children with SCD but low rates of TCD screening, "missed opportunities" for TCD screening may be

numerous. Other areas have successfully utilized the missed opportunity framework to identify opportunities to increase prevention efforts. For example, the immunization literature has a long history of identifying missed opportunities and factors related to missed opportunities.[51,52] Interventions aimed at reducing missed opportunities for vaccination have also been successful.[53,54] In contrast, no study has investigated predictors of missed opportunities for TCD screening among children with SCD, and there are few published intervention studies focused on improving TCD screening in children with SCD. In one example, a comprehensive TCD screening program was implemented at St. Jude Children's Research Hospital which targeted all sickle cell children treated at the hospital. By the third year of the program, 99% of the children identified as at-risk had received at least one TCD screening, showing the effectiveness of an intervention aimed at increasing TCD screening rates.[55] Utilizing the missed opportunity framework for TCD screening is a novel approach to identify opportunities for more targeted interventions which have the potential to increase screening rates among children with SCD.

1.4 Public Health Significance

Pediatric stroke is one of the top ten causes of childhood death in the US and is associated with significant mortality, morbidity, and costs. Children with SCD suffer a disproportionate burden of pediatric stroke. As SCD contributes to the race differences in childhood stroke risk, preventing stroke among this high-risk population may be the only avenue to minimize these disparities. These strokes can be largely prevented through initiation of chronic exchange transfusion therapy after detection of high blood

velocities through TCD screening; however, TCD screening rates are suboptimal among children with SCD. As children with SCD have frequent healthcare encounters but TCD screening remains low, missed opportunities for TCD screening exist. Michigan Medicaid administrative data for a five year time period was utilized to explore the individual- level and area-level predictors of missed opportunities for TCD screening. Additionally, this research explored provider awareness, attitudes and knowledge regarding current recommendations for TCD screening in children with SCD, along with provider perceived barriers of TCD screening. The results of this research could inform the development of targeted interventions at multiple levels (individual, area, provider) aimed at improving TCD screening in this high-risk population.

Table 1.1 Guideline Comparison for Transcranial Doppler Screening Among Children with Sickle Cell Disease

	Age Range for Screening	Type of Sickle Cell	Frequency of Screening if 'Normal'	Definition of 'Normal'
National Heart Lung and Blood Institute (2002)[25]	2 - 16 years	SC-SS	Repeat 3-12 Months	< 200 cm/second
American Academy of Pediatrics (2002)[39]	1 - 13 years		Discuss screening if available	
American Academy of Neurology (2004)[38]	2 years - ?		Optimal Frequency unknown	Mentions STOP cutoff of 200cm/sec
American Heart Association (2006)[37]	2 years - ?	Prevention most important for homozygous	Frequency needed to detect most cases at risk has not been determined; may be performed annually for cases in which the risk of conversion to abnormal is low	Peak systolic velocities of 250cm/sec; 200cm/sec time-averaged means of maximum velocity

Chapter 2

Aim 1: Missed Opportunities for Transcranial Doppler Screening Among Children with Sickle Cell Disease

2.1 Introduction

Pediatric stroke is one of the top ten causes of childhood mortality and is also associated with significant morbidity and cost.[56] Children with SCD are at an increased risk for stroke.[3,4,8] Without intervention, 11% of children with SCD would have been expected to have a stroke by age 20; however, the majority of these strokes are now considered preventable.[27-29] TCD detects blood velocities in cerebral vessels; high velocities are indicative of a high stroke risk and indicate the need to begin preventive efforts in the form of blood transfusions to maintain low hemoglobin concentrations.[30]

The Stroke Prevention in Sickle Cell Anemia (STOP) trial in 1998 found that stroke risk was reduced by 92% in children receiving chronic blood transfusions after detection of high blood velocities by TCD screening as compared to those not receiving transfusions.[24] Given the impact on stroke risk reduction seen in the STOP trial, the NHLBI guidelines recommend that TCD screening be initiated for children with SCD at 2 years old, and if TCD results show normal blood velocities, subsequently receive one screening annually until 16 years old.[25]

Healthcare utilization is often high in children with SCD, as this population has 7-30 times the hospitalization rates, 2-6 times the emergency department visits, and over 8 times the healthcare expenditures compared to their counterparts without SCD.[19,21,57]

This suggests access to health services may not be a substantial barrier to TCD screening.[58] Even with frequent contact with the healthcare system, TCD screening rates are still substantially lower than the goal of each child with SCD having one TCD screening per year, as indicated by the NHLBI guidelines.[41,42] One contributing factor may be missed opportunities for TCD screening, where a child with SCD who is eligible for screening has a health service encounter, yet does not have a TCD screen performed. We hypothesized that missed opportunities for TCD screening may be numerous in children with SCD, given frequent healthcare interactions and low TCD screening rates. The objective of this study was to assess TCD screening rates and the frequency and predictors of missed opportunities for TCD screening in children with SCD. We also estimated the maximum TCD screening rates potentially achievable through reductions of missed opportunities based on these findings.

2.2 Methods

Data Sources

Administrative data from Michigan Medicaid for the years 2007 to 2011 were queried from the Michigan Department of Community Health (MDCH) data warehouse, including enrollment history and claims for inpatient, emergency department, outpatient, and pharmacy services. Michigan Medicaid enrollees were linked to newborn screening results through birth certificates to identify children with SCD born from 1987 to 2008 and all administrative claims were obtained for children with SCD.[59]

Study Population

Inclusion Criteria. Children with SCD were identified as those having hemoglobin (HgB) SS or HgB S/β^0 Thalessemia disease; the former subtype is specifically cited in NHLBI recommendations regarding TCD screening while both variants were included in the STOP trial.[24,25] Children 2 to 16 years old were eligible to be in the study population if they were continuously enrolled in Michigan Medicaid for at least one year from January 1st and December 31st from 2007 to 2011; a one-month gap in enrollment was allowed each year.

Exclusion Criteria. Children with other forms of health insurance were excluded to ensure that all health services received by subjects were completely represented in Medicaid claims. Additionally, children with receipt of 6 or more chronic blood transfusions in a year were excluded since chronic transfusions are likely to be indicative of prior stroke or treatment for children with high blood velocities as detected by previous TCD.[24,30] Blood transfusions were identified through CPT codes of 09882, 09883, 36430, 36455, 86999, S3906, or S9538 on any claim. Children with missing/unknown race or date of birth information were also excluded.

Missed Opportunities for TCD Screening

Two outcomes were identified for each year the child was in the study population: 1) receipt of at least one TCD screening and 2) presence of a missed opportunity for TCD screening. Receipt of TCD screening was defined as having any claim with a CPT code of 93886, 93888, 93890, 93892 or 93893.[60] The proportion of children receiving TCD screening was calculated annually across the study period (2007 to 2011) and by age groups of 2-6 years, 7-11 years, and 12-16 years. A missed opportunity was defined as having an SCD-related healthcare encounter with no receipt of TCD

screening within the same year as defined in a prior study.[61] An SCD-related healthcare encounter was defined as having an ED, inpatient or outpatient visit with an ICD-9 CM diagnosis code for SCD; children with no SCD-related visits were excluded in the consideration of missed opportunities. Consistent with other studies and in an attempt to capture all SCD-related claims, we included diagnosis codes for sickle cell anemia (282.60, 282.61, 282.62) and Hb S/β^0 Thalessemia (282.41 and 282.42), as well as Hb SC (282.63, 282.64), Hb SD (282.68, 282.69).[62-64] The proportion of missed opportunities was calculated annually, for the overall study period, and by age group. The maximum potentially achievable TCD screening rate was estimated for 25%, 50%, 75% and 100% potential reductions in missed opportunities based on TCD screening rates and missed opportunities in 2011. For example, if 300 children were eligible to receive TCD screening, 200 children had a missed opportunity and 40 received TCD screening within a year (TCD screening rate of 40/300 =13%), a 25% reduction in missed opportunities would correspond to an additional 50 children receiving screening in that year. A total of 90 children would then receive screening, corresponding to a screening rate of 30% (90/300).

Correlates of Missed Opportunities

We investigated the correlates associated with a missed opportunity for TCD screening, including: SCD comorbidities (i.e. hypertension, pneumococcal infection, severity of disease[41]), SCD-related healthcare encounters (i.e. ED, inpatient, outpatient and hematologist visits, previous receipt of TCD screening), and demographics of age, sex, and sickle cell type. These comorbidities and healthcare encounters may provide more opportunities to recommend TCD screening and be associated with less missed

opportunities. This phase of the study was restricted to the subset of children continuously enrolled for at least two years (with allowance for a one month gap each year) to assure the covariates occurred prior to the missed opportunity (i.e., to preserve the temporal relationship). With the exception of age, all correlates were characterized in the first year of continuous enrollment and the presence of a missed opportunity was assessed in the following year (year 2 of continuous enrollment). Children with no SCD-related healthcare encounters in year 2 were excluded from this analysis.

SCD Comorbidities. SCD comorbidities were determined from Medicaid administrative claims. Hypertension was indicated by having claims for hypertension medications (drugs in antihypertensive class, excluding Clonidines), an inpatient or outpatient visit for hypertension as identified by claims with an ICD-9 diagnosis code of 401-405, 997.91, or 796.2, or both.[65,66] Pneumococcal infection was identified as any non-preventive healthcare claim with an ICD-9 code of 038.0, 038.2, 481, 482.3, 482.9, or 486. A proxy for severity of disease was determined using the number of inpatient visits per year with children with two or more inpatient visits considered to have greater severity of disease as compared to children with less than two visits.[41]

SCD-Related Healthcare Encounters. ED, inpatient and outpatient (both preventive and non-preventive) visits were identified using the ICD-9 CM codes for SCD. Hematologist visits were defined as having at least one visit with a hematologist as indicated through Medicaid claims. Hematologists were identified through: 1) pediatric hematologists from the American Medical Association (AMA) Masterfile, and 2) an internet search of pediatric hematologists; subsequently, all hematologists were verified as a board certified hematologist using the National Provider Index (NPI).

Previous receipt of TCD screening was identified through CPT codes for TCD as described above and also measured in year 1 of continuous enrollment.

Demographics. Age and sex were from Medicaid eligibility files; age was determined as the child's age on January 1st of the second year of continuous enrollment. Sickle cell type was defined as either Hb SS or Hb S/β^0 Thalessemia using information obtained from Newborn Screening records.

Statistical Analysis. Frequencies and percentages were determined for all demographics, SCD comorbidities, and SCD-related healthcare encounters. Logistic regression with generalized estimating equations (GEE) was used to estimate the association between each covariate and the presence of at least one missed opportunity. GEE models with robust standard errors were estimated to account for the correlation within children, as each child could contribute multiple two-year time intervals.[67] Alternative functional forms for continuous variables were investigated by comparing models with indicator variables (based on quintiles of the distribution) versus continuous variables for SCD-related healthcare encounters or dichotomous versus continuous variables for SCD comorbidities. Based upon the Quasi-Akaike Information Criterion (QIC) for each model, we determined SCD-related inpatient visits, ED visits and age should be modeled as continuous variables, while SCD-related outpatient visits were modeled using indicator variable based upon quintiles (0-1 visits, 2 visits, 3 visits, 4-5 visits, 6+ visits).[67] Hematologist visit, pneumococcal infection, and hypertension were included as dichotomous variables in addition to sickle cell subtype (Hb SS versus Hb S/β^0 Thalessemia), sex (males versus females), severity of disease, and previous

receipt of TCD screening. Covariates showing an association ($p<0.20$) with presence of a missed opportunity were included in the final multivariable model.

The study was approved by the Institutional Review Board of the University of Michigan (#HUM00051878).

2.3 Results

A total of 989 children born between 1987 and 2008 with SCD were identified in Michigan Medicaid claims from 2007-2011. Among these children, 6.4% percent were missing race and date of birth and 19.5% were not continuously enrolled for at least one year across the study period. In total, 329 (33%) met additional eligibility criteria (2-16 years old, less than 6 blood transfusions in a year), contributing 1,024 person-years to this analysis. At baseline (2007), 224 children were continuously enrolled and met eligibility criteria as outlined above. Subsequent years included 216 (2008), 209 (2009), 195 (2010) and 180 (2011) children. Among all 329 eligible children, 73 contributed 1 year of enrollment (22%), 59 children contributed 2 years (18%), 53 contributed 3 years (16%), 46 contributed 4 years (14%) and 98 contributed 5 years of enrollment (30%). The average age in 2007 was 10.5 years (Standard Deviation (SD) 4.1), 50% were female and 87% were sickle cell subtype Hb SS (table 2.1).

TCD Screening and Missed Opportunities

Overall, 140 of 329 eligible children (49%) received screening at least once from 2007 to 2011. Receipt of TCD screening was low each year (10% to 31%), although the proportion of children receiving TCD screening did increase over the study period (figure 2.1). Younger children ages 2-6 years had the highest likelihood of screening

(36%), and rates decreased with increasing age; 20% of children 7-11 years and 14% of 12-16 years received screening from 2007 to 2011.

The number of SCD-related healthcare visits was relatively constant from 2007 to 2011. Each year, children averaged approximately 1 SCD-related inpatient visit, 3 SCD-related outpatient visits, and less than one ED visit (table 2.2). Approximately 12-15% of children did not have an SCD-related healthcare encounter within each year and were excluded from further analysis, resulting in 197 (2007), 188 (2008), 177 (2009), 168 (2010) and 158 (2011) children eligible for quantification of missed opportunities.

The frequency of missed opportunities was high among children without a TCD and having at least one SCD-related healthcare encounter in a given year, ranging from 64% to 89%; 76% of all person-years contained a missed opportunity (figure 2.2). The likelihood of a missed opportunity increased with increasing age, with 59% of children ages 2-6 years, 77% of children 7-11 years and 84% of 12-16 years having at least one missed opportunity over the study period.

Increasing Screening Rates through Reduction of Missed Opportunities

An increase in TCD screening rates could be attained through reductions of missed opportunities. Based on 2011 rates (68% of children had a missed opportunity; 28% of children received TCD screening), a 25% reduction in missed opportunities could correspond to a 42% TCD screening rate among children with SCD. Similarly, a reduction in missed opportunities by 50% could lead to a TCD screening rate of 57%; 75% to a screening rate of 72%, and complete elimination of missed opportunities could lead to a screening rate of 93%.

Correlates of Missed Opportunities

A subset of 270 children (82%) met eligibility criteria previously stated and were continuously enrolled for at least 2 years; 27 (10%) were excluded due to no SCD-related healthcare encounter in the second year of eligibility, resulting in a population ranging from 171 (2007 to 2008) to 146 (2010 to 2011) for this phase of the study. SCD-related healthcare encounters and presence of SCD comorbidities were relatively constant from 2007-2011; the majority had at least one hematologist visit in the first year of continuous enrollment, 10-20% had a pneumococcal infection, and 1-3% had a claim for hypertension medication or a hypertension visit (Table 2.3). Presence of a missed opportunity was associated with age, previous receipt of TCD screening, outpatient visits, inpatient visits, pneumococcal infection, hematologist visit, subtype and severity of disease. When these covariates were included in the multivariable logistic regression GEE model, a one year increase in age was associated with an increased likelihood of a missed opportunity (OR 1.11, CI 1.06, 1.15). Children with previous receipt of TCD screening (OR=0.23, CI: 0.15, 0.38) were less likely to have a missed opportunity than those without a previous screening, along with children with 4-5 outpatient visits (OR=0.44, CI: 0.23, 0.83) or 6 or more outpatient visits (OR=0.25, CI: 0.13, 0.49) compared to children with 0-1 outpatient visits (table 2.4).

2.4 Discussion

TCD screening rates were low in children with SCD in the Michigan Medicaid population, although rates increased over the study period. Low rates of screening combined with frequent interactions with the healthcare system led to a high frequency of missed opportunities for screening, particularly in older children. This study suggests

that even small reductions in missed opportunities could increase TCD screening rates substantially. We estimated that TCD screening rates could potentially more than triple if all missed opportunities were eliminated.

TCD screening rates were low across all ages (10 to 31% from 2007 to 2011), but particularly in teenagers, with only 17% of children ages 12-16 years receiving screening over the study period. Previous studies in sickle cell centers have demonstrated higher overall rates of TCD screening, although a study in a large, managed healthcare plan also showed a trend toward increased screening rates in younger compared with older children. [41,42,45] Our results may be a more accurate reflection of screening rates in all children with SCD due to our inclusion of children up to the age of 16 years, consistent with NHLBI recommendations.[25] Additionally, several studies have used administrative claims for SCD or a recent comprehensive visit for SCD to identify their study populations which biases towards those who seek care and thus may be more likely to receive screening. We included children with minimal or no healthcare for SCD in our calculations by identifying children with SCD through Newborn Screening records, which likely contributed to our lower rates as compared to other studies.

High SCD-related healthcare utilization in Michigan coupled with low rates of TCD screening led to a high frequency of missed opportunities for TCD screening in children with SCD. The increase in missed opportunities in older children may be due in part to variation across guidelines in the ages recommend for TCD screening, which may create confusion for clinicians in regard to screening. While the NHLBI recommends screening from ages 2-16, the American Heart Association (AHA)

suggests screening begin at 2 years with more frequent screening in younger ages, with no specific guidelines for teenagers, and the AAP advises discussion of TCD screening for children ages 1-13 if available.[25,37,39] Our results demonstrating an association between prior receipt of TCD screening and a decreased odds of a missed opportunity also indicate that the same children may be receiving TCD screening each year. These children may have physicians who are consistently recommending TCD screening or there may be other factors, such as patient knowledge of TCD screening, clinic specific recommendation practices, or review of medical chart indicating previous receipt of screening leading to more consistent screening.

We hypothesized that increased ED, inpatient, outpatient and SCD visits and SCD comorbidities would be associated with fewer missed opportunities; however, no associations were found between these potential correlates and missed opportunities, besides with increased outpatient visits. Our association between missed opportunities and increased frequency of outpatient visits is similar to a recent study that showed children with one or more outpatient visits are 2-3 times more likely to receive TCD screening than children without an outpatient visit; however, we did not show a reduction in the odds of a missed opportunity until at least 4 outpatient visits.[45] Other unmeasured factors, such as physician and patient barriers, could be playing a role in missed opportunities aside from the factors investigated in this study. Lack of knowledge and/or awareness regarding TCD screening guidelines among physicians could be contributing to under recommendation for TCD screening and therefore missed opportunities.[68] Patient barriers such as distance to a TCD screening facility and appointment adherence could also play a role in receipt of TCD screening, regardless of

physician recommendation.[41,42,47] Furthermore, caregivers of children with SCD have been shown to perceive the stroke risk for their child to be low and may not realize the importance of TCD screening.[46] Additional research is needed to explore provider and patient-level factors that may influence missed opportunities to identify the most viable intervention targets in this high-risk population.

Strengths of this study include identification of the study population using Newborn Screening records. This allows us to not only identify children with SCD using the gold standard of blood testing, but also allows inclusion of children with no SCD-related healthcare encounters (12-15% per year), which is not possible with children identified with claims data only. Use of the missed framework opportunity framework to identify opportunities for improvement in TCD screening rates is also novel. This framework has been utilized successfully in the immunization literature to identify interventions to increase screening rates,[53,69] but to our knowledge, has never been explored in relation to TCD screening in children with SCD. Additionally, the criteria of full enrollment in Michigan Medicaid and no other forms of health insurance through all parts of the studies ensures full claim history is available for children in the study population.

Limitations to this study also exist. Medicaid claims data were used to identify covariates, including SCD-related healthcare encounters and receipt of TCD screening; therefore, errors in CPT or ICD-9 codes could lead to potential misclassification of these variables. Additionally, if the screening was performed but the child's insurance was not billed for the TCD screening, receipt of TCD screening would have been under reported, resulting in an overstatement of missed opportunities. Our definition of a missed

opportunity cast a wide net and may have not been representative of all situations in which a TCD would normally be ordered. Use of administrative data in this study allowed us to identify receipt of TCD screening, but we were unable to identify reasons for the missed opportunity. Although not all children with SCD are enrolled in Michigan Medicaid, 70% of children with SCD born 1987 to 2008 had a Medicaid ID, indicating that this data does capture the majority of children with SCD in Michigan. Finally, there may be additional children with SCD in Michigan not identified through Michigan's Newborn Screening program; however, through the use of Newborn Screening records, we can accurately report that each child included in the study population did have SCD.

In conclusion, the proportion of children receiving TCD screening each year is low, and missed opportunities are numerous in children with SCD in the Michigan Medicaid population. Increasing age is associated with having a missed opportunity, while 4 or more SCD-related outpatient visits and receipt of TCD screening in the year prior are protective against missed opportunities. Reduction of missed opportunities for TCD screening may be an integral strategy to increase adherence to TCD screening recommendations, thereby reducing the incidence of pediatric stroke in this high-risk population.

Table 2.1 Baseline Demographics of Children with Sickle Cell Disease Continuously Enrolled in Michigan Medicaid in 2007, n=224

	N (%) or Mean (SD)
Age on 1/1/2007 (years)	9.7 (4.2)
Sex	
Male	98 (50%)
Female	97 (50%)
Race	
Black	193 (99%)
White	2 (1%)
Sickle Cell Subtype	
Hb SS	169 (87%)
Hb S/β^0 Thalessemia	26 (13%)

Table 2.2 Healthcare Encounters Among Children with Sickle Cell Disease in Michigan Medicaid Continuously Enrolled for at least 1 year from 2007 to 2011, n = 323

	2007 n = 224	2008 n = 216	2009 n = 209	2010 n = 195	2011 n = 180
SCD-Related Visit			Mean (SD)		
Inpatient	1.2 (1.8)	1.2 (1.9)	1.4 (2.0)	1.1 (1.8)	1.2 (1.9)
Outpatient	3.3 (3.4)	3.4 (3.3)	3.9 (3.7)	3.7 (3.6)	3.7 (3.6)
Emergency Department	0.7 (1.3)	0.7 (1.4)	0.8 (1.3)	0.9 (1.4)	0.8 (1.4)
			N (%)		
No SCD-Related Visits	27 (12%)	28 (13%)	32 (15%)	27 (14%)	22 (12%)

Table 2.3. Healthcare Encounters and Comorbidities of Children with Sickle Cell Disease Continuously Enrolled in Michigan Medicaid for at least 2 years from 2007 to 2011 and with at least 1 Sickle Cell Disease-Related Healthcare Encounter*

SCD-Related Visits	2007-2008 n = 171	2008-2009 n = 156	2009-2010 n = 153	2010-2011 n = 146
			Mean (SD)	
Inpatient	1.3 (1.7)	1.4 (1.8)	1.4 (1.7)	1.3 (1.9)
Outpatient	3.7 (3.5)	4.0 (3.2)	4.1 (3.5)	4.3 (3.6)
Emergency Department	0.7 (1.3)	0.6 (0.9)	0.8 (1.2)	1.0 (1.5)
			N (%)	
Pneumococcal Infection	20 (12%)	27 (17%)	30 (20%)	17 (12%)
Hematologist Visit	151 (88%)	133 (85%)	123 (80%)	119 (82%)
Hypertension Visit	1 (1%)	2 (1%)	0 (0%)	5 (3%)
Hypertension Medication	2 (1%)	2 (1%)	2 (1%)	2 (1%)
Severe SCD	59 (35%)	52 (33%)	59 (39%)	45 (31%)

*Covariates measured in Year 1 of the two years of continuous enrollment

Table 2.4. Multivariable Associations with Presence of a Missed Opportunity for Transcranial Doppler Screening in Michigan Medicaid from 2007 to 2011, n =243

		Odds Ratio	Confidence Interval
SCD-related Outpatient Visits	0-1 visits	Reference	Reference
	2 visits	0.98	0.45, 2.13
	3 visits	0.69	0.33, 1.42
	4-5 visits	0.44	0.23, 0.83
	6+ visits	0.25	0.13, 0.49
Previous TCD Screening	Yes	0.23	0.15, 0.38
	No	Reference	
Age		1.11	1.06, 1.15
Inpatient SCD visit		0.92	0.78, 1.09
Pneumococcal Infection	Yes	0.83	0.47, 1.45
	No	Reference	
Hematologist Visit	Yes	0.85	0.41, 1.76
	No	Reference	
Severity	Yes	1.56	0.80, 3.03
	No	Reference	
Sickle Cell Subtype	Hb S/β^0 Thalessemia	1.39	0.76, 2.54
	Hb SS	Reference	

Figure 2.1 Receipt of Transcranial Doppler Screening Among Children with Sickle Cell Disease Continuously Enrolled in Michigan Medicaid, 2007-2011

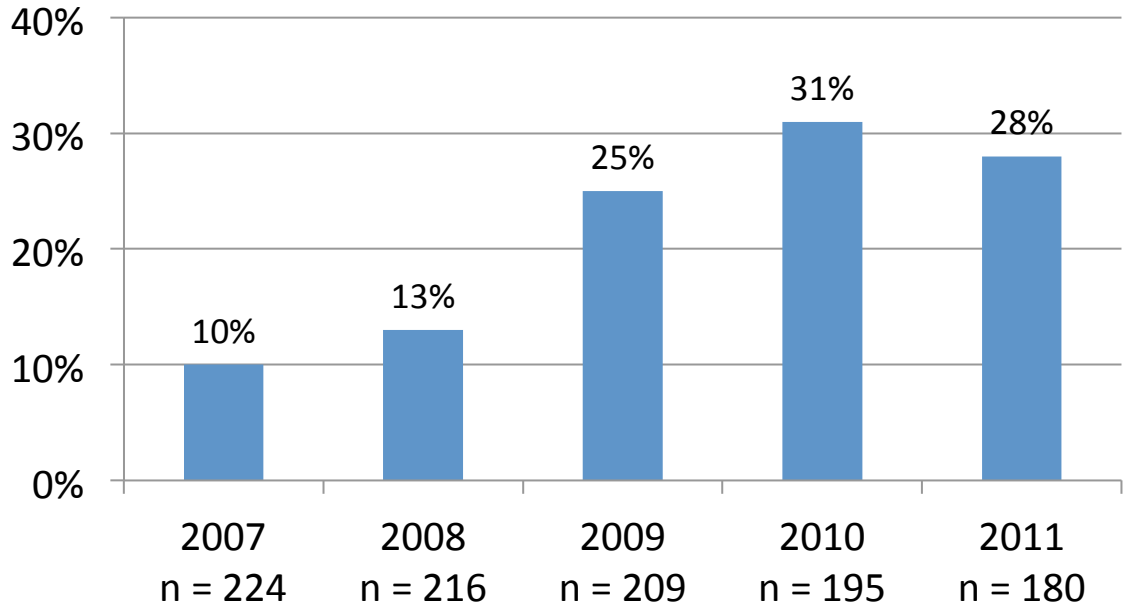
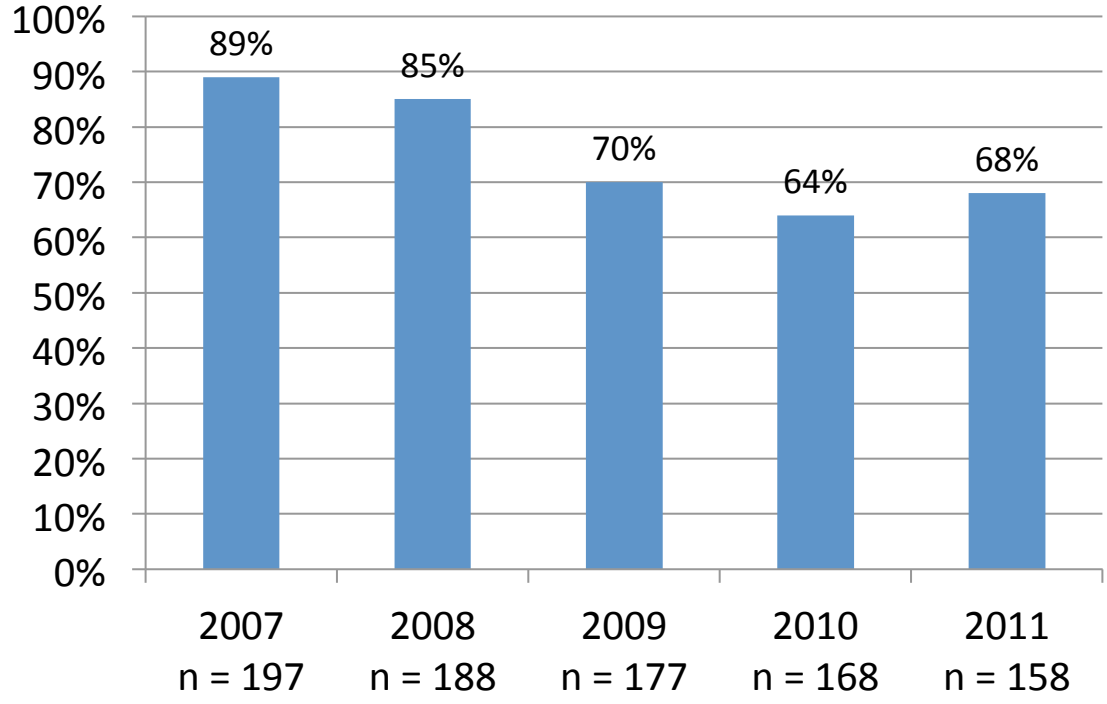


Figure 2.2 Frequency of Missed Opportunities In Children Continuously Enrolled in Michigan Medicaid for at least 1 year from 2007 to 2011 with Sickle Cell Disease and at least 1 Sickle Cell Disease-Related Healthcare Encounter



Chapter 3

Aim 2: The Role of Neighborhoods in the Receipt of Transcranial Doppler Screening Among Children with Sickle Cell Disease

3.1 Introduction

Sickle cell disease (SCD) is a chronic condition causing significant morbidity and mortality exclusively in minority children and is associated with an elevated risk of stroke.[16,17,70] TCD screening is used in these children to detect high blood flow velocities in cerebral vessels which indicate an increased stroke risk and signal the need to initiate chronic blood transfusions as a key stroke prevention strategy.[24,30,32] Once transfusions are initiated, stroke incidence is reduced by up to 90% relative to standard medical care as shown in the 1998 Stroke Prevention Trial in Sickle Cell Anemia (STOP) study. [24]

Although chronic blood transfusion has been known to be an effective stroke prevention strategy since the late nineties, TCD screening rates continue to be low, and few individual-level characteristics impacting screening rates have been identified.[41-43,45] Neighborhood factors have been shown to influence health status among children with chronic conditions; these factors may also influence TCD screening among children with SCD, although this has not yet been explored.[71-73] Neighborhood effects may impact TCD screening through multiple pathways. Residing in a socioeconomically disadvantaged neighborhood has been shown to reduce the likelihood of having a medical home and receiving preventive services, while also increasing the likelihood

that residents of those neighborhoods are unable to obtain healthcare when necessary.[74] Living in a disadvantaged neighborhood leads to higher levels of stress, which is associated with lack of receipt of preventive care.[74] Increased stress is, in turn, connected with depression, anxiety, distress and feelings of powerlessness, all of which may decrease the likelihood of receipt of TCD screening.[75] Individuals residing in disadvantaged neighborhoods may be less likely to participate in health related behaviors due to lower levels of social support.[76,77] Conversely, utilization of preventive services has been shown to be positively correlated with the racial and ethnic composition of the neighborhood.[78] For example, neighborhoods with a greater concentration of African Americans may have increased TCD screening rates compared to neighborhoods with a lesser concentration of African Americans due to the sharing of health related information about SCD given that it predominantly affects those populations.

Identification of neighborhood factors influencing TCD screening could inform the utility of community-level interventions to improve screening rates among children with SCD. With this in mind, our objective was to investigate the geographic variability in TCD screening rates and the role of neighborhood factors in the receipt of TCD screening among children with SCD. We hypothesized there would be a spatial pattern of TCD screening rates across neighborhoods and that living in a socioeconomically disadvantaged neighborhood would be associated with lack of TCD screening. However, the proportion of African American residents within a neighborhood would be associated with increased TCD screening among children with SCD.

3.2 Methods

We used data from Michigan Medicaid to identify presence of a spatial pattern and association of neighborhood-level factors in the receipt of TCD screening among children with SCD residing in Wayne County, Michigan. A large proportion of the county, which includes the City of Detroit, is African American and is home to the majority of children with SCD.

Study Population

Our study population focused on children 2 to 16 years with SCD who resided in Wayne County Michigan. We queried administrative data (inpatient/outpatient claims, enrollment data) from Michigan Medicaid for the years 2007 to 2011 from the MDCH data warehouse. All states perform newborn screening (NBS) to facilitate early identification of SCD upon birth. Using birth certificates, Michigan Medicaid data was linked to NBS data to identify children with SCD.[59]

Inclusion Criteria. We included children with at least one year of continuous enrollment in Michigan Medicaid from January 1st through December 31st from 2007 to 2011 and no other forms of health insurance within this time frame. An allowance for a one-month gap in enrollment each year was made. The addresses for children on January 1st of each year of continuous enrollment were obtained from Medicaid enrollment files. All addresses were geocoded and tied the census tract using geographic identifiers. We included only children with residence in Wayne County, Michigan. We included children ages 2 to 16 years old with hemoglobin (HgB) SS or HgB S/β^0 Thalessemia based on current recommendations for TCD screening from the NHLBI and the sickle cell variants included in the STOP trial.[24,25]

Exclusion Criteria. To exclude children with a potential prior stroke or who were under current treatment for high blood velocities as detected by previous TCD, children with receipt of 6 or more chronic blood transfusions (CPT codes of 09883, 36455, 86999, S3906, S9538, 09882 or 36430 on any inpatient or outpatient claim) in a year were excluded.[24,30] Children missing date of birth information were also excluded.

TCD Screening and Neighborhood Characteristics

Receipt of TCD screening (yes/no) was defined for each child during each year of continuous enrollment as having any claim with a CPT code of 93866, 93888, 93890, 93892 or 93893.[60] Neighborhoods were defined as census tracts, which have been shown to contain generally consistent measures of socio-demographic characteristics of the residents.[79] Neighborhood characteristics from the American Community Survey (ACS) 5 year estimates (2007 to 2011) were linked by census tract to children meeting study eligibility criteria. Neighborhood characteristics considered included the census tract-level percent unemployment, percent African American residents, percent less than high school education and median household income.[71,73]

Statistical Analysis

Frequencies and percentages were determined for demographics of children in the study population and for receipt of TCD screening each year. Means and standard deviations of neighborhood socio-demographic characteristics were calculated across census tracts. The tract-level TCD screening rate was calculated as the total number of person-years containing TCD screening divided by the total number of person-years of children with SCD eligible for screening within each tract. We investigated tract-level TCD screening rates using Global Moran's I with inverse distance.[80] Moran's I

measures spatial correlation and allows evaluation of a spatial pattern across census tracts (i.e., census tracts in close proximity have similar TCD screening rates than those further away).[81] Logistic regression with GEE was used to estimate the association between each neighborhood-level factor and receipt of TCD screening, adjusted for age as a continuous variable. The GEE framework was conducted to account for the correlation within children, as each child could contribute multiple person-years. The model used an exchangeable correlation structure and robust standard errors to assess significance.[82] Independence was assumed for children in the same census-tract, as the small number of person-years within each tract made estimation of within-tract correlation unfeasible.[83] Statistical analyses were performed with SAS 9.2 and ArcGIS 10.1, which was also used for mapping purposes.

The study was approved by the Institutional Review Board of the University of Michigan (#HUM00051878).

3.3 Results

A total of 989 children with SCD born between 1987 and 2008 were identified in Michigan Medicaid claims from 2007 to 2011. Six percent were excluded for missing birthdate or race and 19.5% had no years of continuous enrollment from 2007 to 2011. In total, 329 (33%) met eligibility criteria; 176 of the 329 (54%) children resided in Wayne County during the study period and were included in the analysis. These children collectively contributed 532 person-years. The average age in 2007 was 10.8 years (Standard Deviation (SD) 4), 51% were male, and 94% were sickle cell subtype

Hb SS (table 3.1). The proportion of children receiving TCD screening increased from 2007 to 2011, ranging from 7 to 36% (figure 3.1).

Children in the study population resided in 141 census tracts in Wayne County. Mean percentage of African American residents in the census tract was 80% (SD 28%), percentage of residents with less than a high school education was 27% (SD 18%), percentage unemployed was 27% (SD=10%), and the mean household income was $31,040 (SD $12,091). Number of person-years within each census tract ranged from 1 to 14, with a median of 3 (Interquartile Range (IQR) 2 to 5). The proportion of children receiving TCD screening within census tracts ranged from 0 to 100%, with a median of 0% and a mean of 19% (SD 29%, IQR 29%) (Figure 3.2). Overall, 60% of neighborhoods (n=85) had screening rates of 0%, and 71% (n=114) had screening rates less than 50%. Investigation of spatial correlation failed to provide any evidence of a spatial pattern of TCD screening across the census tracts in Wayne County (Moran's I z-score -0.94, p-value 0.35). No associations were found between the neighborhood characteristics and receipt of TCD screening among children with SCD (Table 3.2).

3.4 Discussion

TCD screening rates in Michigan are low among children in Wayne County, Michigan (7 to 36%) and across census tracts in Wayne County, show no spatial pattern, and were not found to be associated with neighborhood socio-demographic characteristics. The lack of variability in screening rates across neighborhoods may indicate that interventions targeting the entire population of children with SCD as

opposed to particular neighborhoods are necessary to increase TCD screening rates in this high-risk population.

The lack of association between neighborhood characteristics and TCD screening in our study population may be partially due to the low TCD screening rates and high levels of neighborhood disadvantage in Wayne County. TCD screening rates were low across all census tracts, with a median of 0%. Additionally, the socioeconomic characteristics of the neighborhoods where children with SCD resided were indicative of a high level of disadvantage. Using American Community Survey 2007 to 2011 estimates, the mean rate of unemployment across our census tracts in Wayne County was 27% versus 8.7% in the US, median household income was $31,040 versus $52,762 in the US, and the mean percentage less than high school education was 27% in our census tracts versus 8.5% in the US.[84] These neighborhoods are also more disadvantaged than Wayne County as a whole, an area reflective of other urban populations with a large percentage of African Americans, reporting nearly 10% higher unemployment (Wayne County: 17.4%), $10,000 lower median household income (Wayne County: $41,886), and 16% less residents with less than a high school education (Wayne County: 11.5%). These statistics show the census tracts where children with SCD reside in Wayne County are at a severe socioeconomic disadvantage compared to the rest of the US.

Strengths of this study include identification of the study population using Newborn Screening records. This allowed us to identify children with SCD using the recognized gold standard, blood testing, along with the criterion of continuous enrollment to ensure full capture of all healthcare claims. However, there are also

limitations to this study. Addresses of children were assessed on January 1st of each year of continuous enrollment. Children may have moved in or out of Wayne County within the year, and been inappropriately included, excluded, or attributed to the incorrect neighborhood based on their address. Identification of neighborhoods using census tracts is a crude measure of neighborhood and may not be reflective of the true boundaries that define the residence of children with SCD. The ACS estimates used may introduce bias as 5 year estimates were used. These estimates refer to the socio-demographic characteristics over the entire study period and may not be reflective of the tract-level characteristics each year. The neighborhood variables in this analysis may not have accurately captured the socio-cultural and economic variability of the neighborhoods. Additional neighborhood variables may influence TCD screening, such as availability of medical resources, neighborhood safety, and reliability of public transportation, which were not considered. Additionally, receipt of TCD screening was determined using Medicaid administrative claims, which may be incomplete and/or inaccurate. Only children enrolled in Michigan Medicaid were included; however, 70% of children born in Michigan with SCD have a Medicaid ID suggesting these cases are generally representative of the population of children with SCD in Michigan. Further, the sample size was low for this study; adequate power to detect spatial correlation with this data may not have been present.

In conclusion, our results did not show that neighborhoods play a role in the receipt of TCD screening among children with SCD in Wayne County enrolled in Michigan Medicaid, indicating that additional barriers to screening may exist among patients and providers, and further investigation of correlates of TCD screening is

necessary. Strategies are clearly needed to improve the translation of the clinical trial evidence supporting TCD screening to the population in this geographic area to reduce the incidence of stroke.

Table 3.1. Baseline Demographics of Children with Sickle Cell Disease in Michigan Medicaid Continuously Enrolled for at least 1 Year from 2007 to 2011 and Residing in Wayne County, Michigan (2007, n=123)

	N (%) or Mean (SD)
Age on 1/1/2007 (years)	10.8 (4.0)
Sex	
Male	63 (51%)
Female	60 (49%)
Sickle Cell Subtype	
HgB-SS*	116 (94%)
HgB-Beta Thalessemia*	7 (6%)

Table 3.2. Neighborhood Level Factor Associations with Receipt of Transcranial Doppler Screening Among Children with Sickle Cell Disease in Michigan Medicaid Residing in Wayne County, 2007 to 2011*

	Odds Ratio; 75th vs. 25th percentile	Confidence Interval
% Unemployment	0.98	0.67, 1.43
% African American Residents	0.97	0.82, 1.15
% Less than High School Education	1.27	0.86, 1.86
Median Household Income	0.97	0.70, 1.33

*Adjusted for age

Figure 3.1. Transcranial Doppler Screening Rates Among Children with Sickle Cell Disease Continuously Enrolled in Michigan Medicaid for at least one year from 2007 to 2011 and Residing in Wayne County

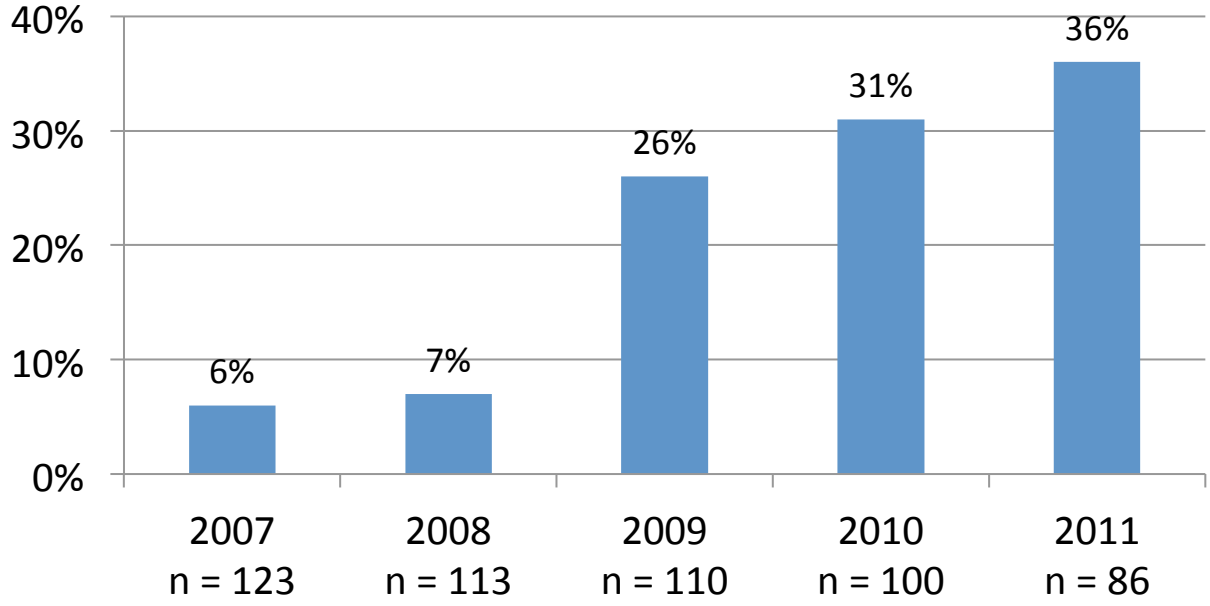
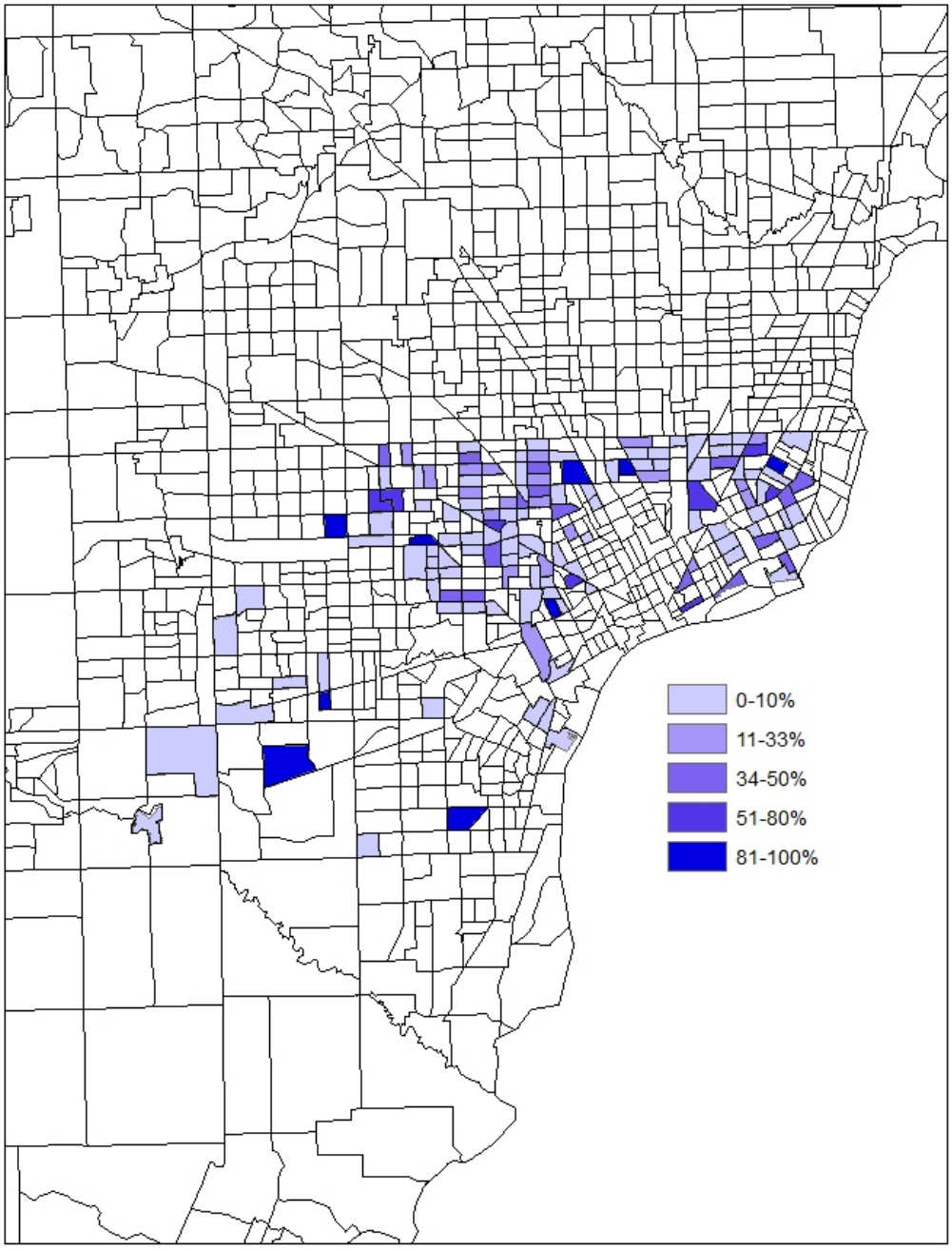


Figure 3.2. Tract-Level Transcranial Doppler Screening Rates in Wayne County, Michigan, From 2007 to 2011



Chapter 4

Aim 3: Factors Influencing Physician Adherence to Transcranial Doppler Screening in Sickle Cell Disease

4.1 Introduction

Sickle cell disease (SCD) is a chronic condition with extensive morbidity that exclusively affects minority children and increases the risk of stroke, a leading cause of childhood death and disability.[16,17,70] Historically, approximately 11% of children with SCD had a stroke by age 20; however, many of these strokes are now preventable.[24,28,29,70] TCD screening is used to detect high blood flow velocities in cerebral vessels which indicate an increased stroke risk and signal the need to initiate chronic blood transfusions as a key stroke prevention strategy.[24,30,32] The Stroke Prevention Trial in Sickle Cell Anemia (STOP), published in 1998, showed once transfusions are initiated, stroke incidence is sharply reduced by up to 90% relative to standard medical care.[24]

Given its importance as a stroke prevention strategy, numerous national organizations have released guidelines recommending TCD screening among children with SCD. However, these guidelines differ substantially in key areas, with the NHLBI providing the most specific guidelines.[25,37,39] Adherence to clinical practice guidelines has been demonstrated to be beneficial in improving health outcomes for patients across many specialties.[85-89] Despite these findings, physician adherence to guidelines remains low, particularly in the clinical specialty of pediatrics.[90-94] Ambiguities and

differences in these guidelines may lead to variability in physicians' recommendation of TCD screening among children with SCD, as suggested by the low rates of screening observed in numerous settings.[41-43,45]

Importantly, children with SCD have significantly higher healthcare utilization than children without SCD, indicating that opportunities for recommending TCD screening exist.[20] Because the degree of physician adherence to TCD screening guidelines may influence screening rates, our objective was to explore factors that may be related to adherence such as physicians' awareness, attitudes and knowledge of TCD screening guidelines for children with SCD. We also assessed physician-perceived external barriers to administration of TCD screening in children with SCD among primary and specialty care physicians.

4.2 Methods

Study Population

Pediatric hematologists, pediatric neurologists and primary care physicians (PCPs) were chosen as the study population as these physicians would be most likely to treat children with SCD. Pediatric hematologists and pediatric neurologists (n=250 each due to cost limitations) were randomly sampled across the US (due to insufficient numbers of these specialties in the state of Michigan) from the American Medical Association (AMA) Physician Masterfile. The AMA Masterfile is a continuously updated list of all physicians in the US which includes both members and nonmembers of the AMA. PCPs were identified as physicians with a certification in general pediatrics, family medicine or adolescent medicine treating children with SCD. To increase the likelihood

of the physician treating a child with SCD, PCPs were included if they had one or more Michigan Medicaid claims reporting an ICD-9 CM diagnosis code for SCD from 2008-2012 (n=206). Consistent with other studies, we included diagnosis codes for sickle cell anemia (282.60, 282.61, 282.62), Hb SC (282.63, 282.64), Hb SD (282.68, 282.69), and Hb S beta thalassemia (282.41 and 282.420); we did not include cases reporting sickle cell trait (282.5) or other hemoglobinopathies.[62-64] Medicaid claims for states other than Michigan were not available to identify physicians treating children with SCD in these states.

Survey Development, Content and Administration

The physician survey was developed by the lead author and revised based on input from the research team. Elements of the survey were chosen based off the framework presented by Cabana et al, which organized physician barriers into seven major categories.[95] Our survey content was developed based on factors hypothesized to influence physician adherence to TCD guidelines specifically and included the following: physician (internal) barriers (awareness, attitudes and knowledge of guidelines), physician-perceived external barriers, and physician and practice characteristics (figure 4.1, adapted from Cabana et al).[95] Our full survey instrument is provided in Appendix 4.1.

Awareness of TCD screening guidelines was assessed through questions about familiarity and accessibility of national guidelines for TCD screening. Attitudes regarding TCD screening for children with SCD were assessed through agreement with a series of statements regarding outcome expectancy (SCD stroke risk, predictive value of TCD results, chronic exchange transfusion), perception of guidelines (strength of evidence,

conflicting guidelines), and self-efficacy (comfort caring for children with SCD and with TCD screening, ability to reduce stroke risk). Knowledge of TCD screening guidelines for children with SCD was assessed through a series of multiple choice and open ended questions regarding types of SCD to be included for screening, ages to initiate and terminate screening, and actions to take based on TCD screening results. Correct responses to knowledge questions were based on agreement with NHLBI guidelines for treatment of children with SCD, as these guidelines are the most specific regarding TCD screening among children with SCD and are often used as guidelines for clinics developing TCD screening programs.[25,55] Physician-perceived external barriers to TCD screening focused on agreement with statements in three main areas: access/environmental barriers, patient barriers and administrative barriers. Level of agreement with each attitude and external barrier statement was assessed using a 5-point Likert scale: strongly disagree (1) to strongly agree (5). Physician and practice characteristics were assessed through multiple choice and open ended questions regarding physician sex, race, ethnicity, age, years of practice, specialty, hours of general continuing medical education, patient characteristics, and practice affiliation.

The survey was piloted for content and clarity with at least one physician from each specialty and questions were modified prior to administration based on feedback. The survey was administered via priority mail in May 2012 with a $2 incentive included. A follow-up mailing was conducted among non-respondents without an incentive in June 2012. Survey collection was closed on December 31, 2012.

Eligibility

Physicians in the study population were eligible to complete the survey if the survey was deliverable and if they indicated on the survey that s/he currently provided care for children with SCD. All eligible physicians were asked to answer questions regarding attitudes and perspectives on TCD screening and physician and practice characteristics. Physicians who believed patients with SCD should receive TCD screening (92%) were then asked to answer questions regarding knowledge of specific guidelines and physician perceived external barriers, as these physicians would be the most appropriate recipients of interventions aimed at increasing adherence to screening guidelines.

Statistical Analysis

Means and standard deviations (SD) or frequencies and percentages were calculated for physician and practice demographics. Responses regarding attitudes toward guidelines regarding TCD screening and external barriers were collapsed into categories of agree (strongly agree or agree) or disagree (strongly disagree, disagree, neutral) and compared across specialties using chi-square tests. Knowledge of specific NHLBI guidelines was calculated as the proportion of questions answered correctly (6 knowledge questions were included in the survey) and compared across specialties using Fisher's exact tests due to small sample size. Frequencies of responses for all other questions were calculated overall and by specialty.

The study was approved by the Institutional Review Board of the University of Michigan (#HUM00052547).

4.3 Results

A total of 706 physicians were sent surveys; 65 were undeliverable, 8 physicians had retired, and 276 were returned by the respondent (44% response rate among deliverable surveys). Among the 276 respondents, 141 (51%) physicians currently treated children with SCD (28% PCPs, 21% pediatric neurologists, and 51% pediatric hematologists). Among these physicians, 61% were male, 73% were white, 18% Asian or Pacific Islander, 4% black, and 4% other, and 4% were of Hispanic origin. The average respondent was 52 years old (Standard Deviation (SD) 11 years) and had been practicing for 19 years (SD 12 years). The respondents varied by self-reported hours of general continuing medical education per month, the proportion of pediatric patients with SCD, the proportion of pediatric patients covered by Medicaid, and number of pediatric patients seen per year; the majority (66%) worked at a university, hospital or medical center (Table 4.1). Overall, 127 (92%) out of the 141 respondents who treat children with SCD believed that children with SCD should receive TCD screening (82% PCPs, 90% pediatric neurologists, 99% pediatric hematologists) and of these, 97 (72%) currently recommend screening to their patients (34% PCPs, 64% pediatric neurologists, 94% pediatric hematologists). Reasons for not recommending TCD screening included referring the patient to a hematologist (n = 17), another doctor (n = 2) or a sickle cell center (n = 4) for screening, or lack of familiarity with guidelines (n = 6).

Internal Barriers - Awareness

Sixty-seven percent of eligible respondents indicated they were extremely, very, or moderately familiar with national guidelines regarding TCD screening among children with SCD, and 33% indicated they were slightly or not at all familiar. Familiarity varied

across specialty, with 30% of PCPs, 61% of pediatric neurologists and 90% of pediatric hematologists indicating they were extremely, very or moderately familiar with TCD screening guidelines ($p<0.0001$). If more information was needed regarding TCD screening among children with SCD, 66% of respondents indicated they would refer to the AAP, 44% the NHLBI, 35% Up To Date Inc (an online, evidence-based clinical support resource), 26% the AAN, and 5% the AHA. Other sources of information included the American Society of Hematology (n = 5), other doctors or centers (n = 5) or research papers, textbooks, other websites or guidelines (n = 8).

Internal Barriers - Attitudes

Attitudes regarding TCD screening among children with SCD differed depending on the statement and among specialties. Table 4.2 lists each perspective statement, along with the proportion of physicians who agreed with the statement by specialty. Most physicians felt comfortable caring for children with SCD and believed these children have a high risk of stroke. Additionally, most had positive perceptions of guidelines with few indicating that guidelines were based on questionable evidence or that conflicting guidelines existed. The majority (64%) of PCPs did not feel well informed regarding TCD guidelines, whereas only 28% of pediatric neurologists and 7% of hematologists did not feel well informed ($p<0.0001$). Self-efficacy questions revealed similar specialty patterns, with PCPs feeling more uncomfortable discussing risks and benefits of TCD screening with patients and families and their ability to reduce stroke risk in patients with SCD in comparison to pediatric neurologists and hematologists. The vast majority of physicians would recommend chronic exchange transfusion based on

abnormal TCD results (95% PCPs, 99% pediatric neurologists and 93% pediatric hematologists).

Internal Barriers - Knowledge

Among physicians who believe children with SCD should receive TCD screening (n=127), the proportion of knowledge questions answered correctly based on NHLBI guidelines was low. Overall, the question with the highest percentage of correct responses was the age to begin TCD screening (35% correct), and the lowest was actions to take upon an abnormal TCD screening result (13% correct). Percentage of correct responses differed among specialty, with PCPs and pediatric neurologists consistently scoring lower than pediatric hematologists (Table 4.3).

External Barriers

Two physician-perceived external barriers were reported by the majority of physicians to hinder receipt of TCD screening; distance to a vascular laboratory (51%) and low patient adherence to TCD appointments (56%). In general, PCPs selected more barriers than pediatric neurologists or hematologists. Physician-perceived external barriers differed across specialties for the majority of barriers (Table 4.4).

4.4 Discussion

Abnormal TCD results in children with SCD are associated with a high risk of stroke and should prompt stroke prevention efforts in the form of chronic blood transfusions. Although the effectiveness of blood transfusion for stroke prevention has been known since the late nineties, rates of TCD screening among children with SCD have remained low.[24,41] Physicians' awareness, attitudes and knowledge of TCD

guidelines for children with SCD may influence physician recommendation of TCD screening; however, no study has investigated these internal factors. In our study, the majority of physicians believed children with SCD have a high risk of stroke and should receive TCD screening, but familiarity with guidelines, self-efficacy and knowledge of NHLBI-specific guidelines were low, particularly among PCPs, and differed considerably by specialty. Additionally, we identified distance from child's home to a vascular laboratory and patient adherence to appointments as physician-perceived external barriers.

Among attitudes regarding TCD guidelines, self-efficacy (comfort discussing risks and benefits of TCD screening and blood transfusions, ability to reduce stroke risk among patients) and outcome expectancy (TCD predicts stroke risk, blood transfusions reduce stroke risk) showed the largest specialty differences, with PCPs and pediatric neurologists consistently rating themselves lower in these categories than pediatric hematologists. However, the overall proportion of physicians with high self-efficacy and outcome expectancy was still low, indicating a need for improvement in these areas across all specialties. Interventions focusing on improving self-efficacy among physicians, such as educational toolkits, formal clinical training and increased availability of educational resources, have been successful in increasing confidence and knowledge among physicians across the board.[68,96,97] As most physicians felt comfortable caring for children with SCD, these educational interventions might be best focused on increasing physician knowledge of the risks and benefits of TCD screening and blood transfusions, as these were areas in need of improvement among all physicians. These educational targets are in line with the SCD-related research agenda

released by the NHLBI which identified clear, evidence based guidelines for physicians as a priority,[98] and numerous quality improvement collaborations focused on improving care and outcomes among children with SCD.[99] Impacting attitudes through enhancement of knowledge and confidence may positively affect adherence to guidelines, especially among PCPs and pediatric neurologists, although this requires further study.

With regard to knowledge, questions about next steps for abnormal TCD results were answered incorrectly with the highest frequency. This indicates the need for increased physician education regarding actions to take based on TCD screening results since these actions are the basis for stroke prevention efforts. Also, questions about ages to begin and end screening were answered incorrectly by the majority of respondents which could potentially lead to differential TCD screening rates by age. As hematologists' knowledge and familiarity regarding guidelines was higher than neurologists and PCPs, increased referral by other physicians to hematologists could be an important driver of increased TCD screening. This may be especially true considering only one third of PCPs reported recommended screening to their patients and the majority of PCPs who did not recommend screening referred the patient to a hematologist for TCD screening. Since treatment guidelines for children with SCD recommend frequent contact with hematologists, patient adherence to these specialist appointments may be integral to increasing TCD screening rates. However, it may also be important to continue to increase knowledge of TCD guidelines among PCPs, as not all children will see a hematologist each year. Although hematologists did answer the knowledge questions correctly with the highest frequency, the proportion of correct

answers among hematologists was low. There is still substantial room for improvement in their knowledge of specific guidelines, particularly if they are perceived as the primary initiator of TCD screening among children with SCD.

Our survey showed the AAP to be the most common source referenced for information regarding TCD screening. These guidelines are the most ambiguous given their recommendation that TCD screening should be discussed, if available.[39] While both the NHLBI and AHA strongly recommend TCD screening, their respective guidelines differ with regard to recommended ages for screening, frequency of screening and actions to be taken based on screening results.[25,37] The AAP's more ambiguous recommendation has provoked controversy among pediatricians who feel stronger guidelines are warranted.[40] We used the NHLBI guidelines as the standard for knowledge which may have influenced our results with respect to the proportion of correct answers. These guidelines are used as the basis for TCD screening in numerous clinics.[42,55]

Few studies exist regarding physician-perceived external factors that may influence TCD screening rates. We found that physicians perceive lack of adherence to appointments and distance to a vascular laboratory to be barriers to the receipt of TCD screening. Data from a recent study showed 72% of hematologists identified patient adherence to appointments to be a barrier to TCD screening.[47] The finding that distance to a vascular lab may be a barrier is also supported by research in a large, managed healthcare plan that found living within 30 miles of a vascular laboratory was the only independent predictor for receipt of TCD screening.[41] One option to address this particular barrier to TCD screening could include offering TCD screening onsite at

hematology clinics, as this eliminates travel to a vascular laboratory and has been shown to increase screening rates.[55] Although both this study and ours indicated that physicians perceive patient oriented issues to be the main barriers to receipt of TCD screening, lack of knowledge and self-efficacy are perceived by caregivers as greater barriers to screening than practical issues such as transportation and appointment adherence.[46] The disagreement between patient and provider perceptions of barriers to TCD screening indicates that further study is necessary among both patient guardians and providers to identify which external factors influence screening rates in order to develop interventions that focus on the correct targets.

Some limitations of this work warrant discussion. The main limitation for this study is the 44% response rate among physicians; however, this response rate is in line with other physician survey response rates.[100-102] Non-response rates among deliverable surveys were similar across specialties, with 58% of PCPs, 58% of pediatric neurologists and 54% of pediatric hematologists not returning deliverable surveys. The AMA Masterfile as a source to identify all pediatric hematologists and neurologists in the United States may have been incomplete and not included all specialists. As the survey was focused on self-report, bias may exist on multiple aspects of the survey, such as awareness and attitudes regarding screening practices. Use of PCPs only in the state of Michigan may limit the generalizability. Also, we did not investigate physician initiation of blood transfusion for patients regardless of TCD screening. It is possible that some doctors begin stroke prevention efforts without prior use of TCD results, although this would not be consistent with current guideline recommendations. Given the results of our survey, we were unable to determine if the existence of multiple guidelines, lack of

physician adherence to guidelines, or other factors are contributing to the low screening rates; however, we were able to identify factors that may affect adherence for future intervention targets.

Factors such as awareness, attitudes and knowledge of specific guidelines may influence physician adherence to TCD screening recommendations. Additional research regarding these barriers is necessary to understand their role in physician recommendation of TCD screening, specifically in the areas of physicians' lack of self-efficacy and knowledge of recommendations as we found these to be low across all specialties. This additional research could assist in the development of targeted interventions to increase TCD screening among children with SCD. As significant differences were found among specialties, specialty-specific education may be important to improve TCD screening rates; however, substantial room for improvement exists across all specialties. Targets for increasing TCD screening among children with SCD must continue to be identified in order to prevent the devastating consequences of stroke in this high-risk population.

Table 4.1. Characteristics of Physicians Treating Children with Sickle Cell Disease Responding to Survey, , n = 141

		N (%)
Sex	Male	84 (60%)
	Female	53 (38%)
Race	White	99 (70%)
	Black	6 (4%)
	Asian / Pacific Islander	24 (17%)
	Other	6 (4%)
Ethnicity	Non-Hispanic	126 (89%)
	Hispanic	5 (4%)
Age		52 (11) years
Practice Years		19 (12) years
Specialty	Pediatric Hematology	72 (51%)
	Pediatrics/Family Medicine (PCPs*)	40 (28%)
	Pediatric Neurology	29 (21%)
Hours of CME per month*	>1 hour	3 (2%)
	1-5 hours	81 (57%)
	More than 5 hours	55 (39%)
Pediatric Patients With Sickle Cell Disease	>5%	78 (55%)
	5-10%	24 (17%)
	11-20%	14 (10%)
	More than 20%	22 (16%)
Pediatric Patients Covered By Medicaid	>5%	7 (5%)
	5-24%	19 (13%)
	25-49%	41 (29%)
	More than 50%	65 (46%)
Primary Practice Ownership	Private office	21 (15%)
	University/hospital/medical center	91 (65%)
	Practice Network	10 (7%)
	Sickle Cell Center	13 (9%)
	Combination	2 (1%)
Pediatric Patients Per Year	1-500	34 (24%)
	501-1500	53 (38%)
	1501-3000	37 (26%)
	More than 3000	14 (10%)

* PCP: Primary Care Physicians; CME: Continuing Medical Education

Table 4.2. Agreement with Physician Perceptions and Attitudes Regarding Transcranial Doppler Screening, n = 141

	N (%)				
Statement	**Overall***	**Primary Care Physicians* n = 40**	**Pediatric Neurology* n = 29**	**Pediatric Hematology* n = 72**	**p-value***
I feel comfortable caring for children with sickle cell disease.	119 (86%)	28 (71%)	20 (71%)	71 (99%)	<0.001
Children with sickle cell disease have a high risk of stroke.	130 (93%)	34 (87%)	29 (100%)	67 (93%)	0.13
I do not feel well informed regarding Transcranial Doppler ultrasonography guidelines for children with sickle cell disease.	38 (27%)	25 (64%)	8 (28%)	5 (7%)	<0.001
I do not feel comfortable discussing risks and benefits of Transcranial Doppler ultrasonography with my patients and their families.	36 (26%)	21 (54%)	7 (24%)	8 (11%)	<0.001
Guidelines for Transcranial Doppler ultrasonography for children with sickle cell disease are based on questionable evidence.	7 (5%)	5 (13%)	0 (0%)	2 (3%)	0.02
There are conflicting guidelines regarding Transcranial Doppler ultrasonography for children with sickle cell disease.	15 (11%)	7 (18%)	3 (10%)	5 (7%)	0.18
Transcranial Doppler ultrasonography results predicts stroke risk.	96 (69%)	14 (37%)	17 (59%)	65 (90%)	<0.001
I am confident in my ability to reduce the risk of stroke in my patients with sickle cell disease.	68 (49%)	6 (16%)	12 (41%)	50 (69%)	<0.001
I will not recommend chronic exchange transfusion regardless of Transcranial Doppler ultrasonography results.	5 (4%)	2 (5%)	2 (7%)	1 (1%)	0.34
Chronic exchange transfusion is effective at reducing stroke risk among children with sickle cell disease.	108 (78%)	18 (46%)	24 (83%)	66 (93%)	<0.001
Hydroxyurea is effective at reducing stroke risk among children with sickle cell disease.	54 (39%)	17 (44%)	10 (36%)	27 (39%)	0.79

I am comfortable discussing the risks and benefits of chronic exchange transfusion with my patients and their families.	89 (64%)	13 (33%)	10 (34%)	66 (93%)	<0.001

*Up to 4 physician responses missing (varies by statement)
**P-value comparing % agreement across physician specialties

Table 4.3. The Proportion of Knowledge Questions Answered Correctly based on National Heart Lung and Blood Institute Guidelines, n=127

Knowledge Topic	Overall	Primary Care Physicians n = 31	Pediatric Neurologist n = 26	Pediatric Hematologist n = 70	p-value*
Age to Begin TCD Screening	35%	16%	12%	53%	<0.001
Age to End TCD Screening	20%	3%	8%	33%	<0.002
Sickle Cell Subtypes to Screen	31%	13%	0%	50%	<0.003
Actions to take with Normal TCD Result	31%	10%	15%	46%	<0.004
Actions to take with Conditional TCD Result	22%	10%	12%	33%	<0.005
Actions to take with Abnormal TCD Result	13%	3%	4%	20%	0.002

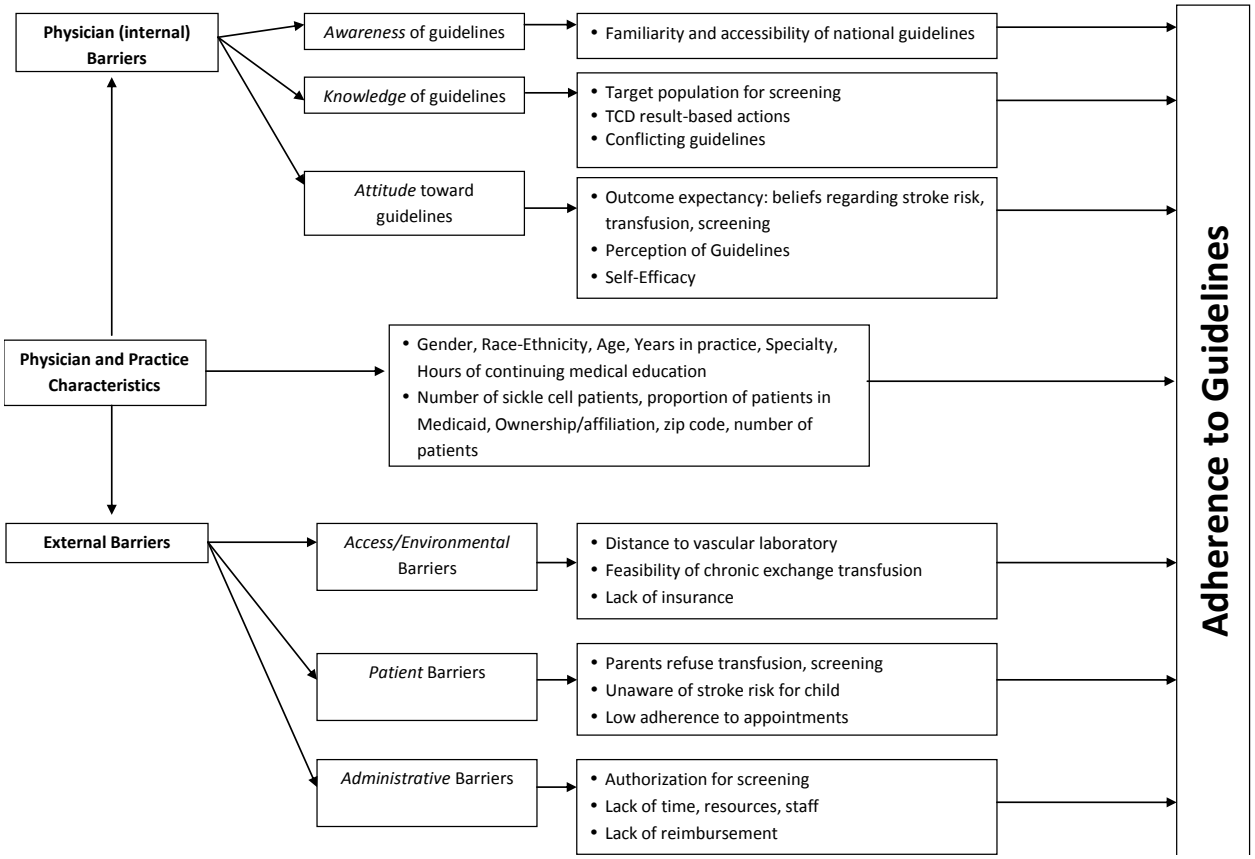
*P-value comparing % correct across physician specialties

Table 4.4 Agreement with Physician-Perceived Barriers for Receipt of Transcranial Doppler Screening, n = 127

	N (%) Agree with statement				
Statement	**Overall Agreement***	**Primary Care Physicians* n = 31**	**Pediatric Neurology* n = 26**	**Pediatric Hematology* n = 70**	**p-value***
Distance from patients' homes to vascular laboratories is a barrier to receipt of Transcranial Doppler ultrasonography.	64 (51%)	19 (63%)	7 (27%)	38 (54%)	0.02
Authorization from private insurance carriers is a barrier to receipt of Transcranial Doppler ultrasonography.	38 (30%)	15 (50%)	10 (38%)	13 (19%)	0.004
Authorization from Medicaid is a barrier to receipt of Transcranial Doppler ultrasonography.	26 (21%)	11 (37%)	7 (27%)	8 (11%)	0.01
Lack of time/resources to describe risks and benefits to my patients and families is a barrier to receipt of Transcranial Doppler ultrasonography.	25 (20%)	16 (53%)	4 (15%)	5 (7%)	<0.001
Parental refusal is a barrier to receipt of Transcranial Doppler ultrasonography.	32 (26%)	12 (40%)	3 (12%)	17 (24%)	0.06
Reimbursement from private insurance carriers is a barrier to receipt of Transcranial Doppler ultrasonography.	28 (22%)	15 (50%)	8 (31%)	5 (7%)	<0.001
Reimbursement from Medicaid is a barrier to receipt of Transcranial Doppler ultrasonography.	22 (18%)	10 (33%)	8 (31%)	4 (6%)	<0.001
Lack of appropriate staff to interpret results is a barrier to receipt of Transcranial Doppler ultrasonography.	26 (21%)	7 (23%)	7 (27%)	12 (17%)	0.53
Low patient adherence to appointments is a barrier to receipt of Transcranial Doppler ultrasonography.	70 (56%)	18 (60%)	6 (24%)	46 (66%)	0.001
Lack of insurance is a barrier to receipt of Transcranial Doppler ultrasonography.	40 (32%)	15 (50%)	8 (31%)	17 (24%)	0.04
Lack of parental belief that their child is at an increased risk for stroke is a barrier to receipt of Transcranial Doppler ultrasonography.	51 (41%)	14 (47%)	10 (38%)	27 (39%)	0.73

*Up to 3 physician responses missing (varies by statement)
**P-value comparing % correct across physician specialties

Figure 4.1. Potential Factors Influencing Physician Adherence to Transcranial Doppler Screening Guidelines*



*adapted from Cabana et al[95]

Appendix 4.1 Survey Instrument

☐☐☐☐

1. Do you currently provide care for children (18 years of age and younger) with sickle cell disease?

   ☐ Yes→Continue with survey ☐ No→STOP and return survey in provided envelope. **Thank you!**

2. *The following statements ask about your perspectives regarding practice guidelines in general. Rate your agreement with each statement from strongly disagree to strongly agree by checking the box that corresponds to your answer.*

Statement	1 Strongly Disagree	2 Disagree	3 Neutral	4 Agree	5 Strongly Agree
a. Practice guidelines are too prescriptive.					
b. Generally, practice guidelines are cumbersome and inconvenient.					
c. Practice guidelines improve patient outcomes.					
d. The cost of following practice guidelines outweighs the benefits.					
e. Practice guidelines interfere with my professional autonomy.					
f. Practice guidelines help standardize care and ensure patients are treated in a consistent way.					
g. Practice guidelines are difficult to apply to my specific practice.					

3. To what degree are you familiar with national guidelines (for example, the American Academy of Pediatrics) regarding transcranial Doppler ultrasonography among children with sickle cell disease?

   ☐ Extremely familiar ☐ Very familiar ☐ Moderately familiar ☐ Slightly familiar ☐ Not at all familiar

4. If you needed more information regarding transcranial Doppler ultrasonography among children (18 years of age and younger) with sickle cell disease, what organizational guidelines would you refer to (check all that apply)?

   ☐ American Heart Association ☐ American Academy of Neurology

   ☐ American Academy of Pediatrics ☐ National Heart, Lung and Blood Institute

   ☐ Up To Date Inc ☐ Other (specify): _____

5. *The following statements ask about your perspectives regarding guidelines for transcranial Doppler ultrasonography among children with sickle cell disease. Rate your agreement with each statement from strongly disagree to strongly agree by checking the box that corresponds to your answer.*

Statement	1 Strongly Disagree	2 Disagree	3 Neutral	4 Agree	5 Strongly Agree
a. I feel comfortable caring for children with sickle cell disease.					
b. Children with sickle cell disease have a high risk of stroke.					
c. I do not feel well informed regarding transcranial Doppler ultrasonography guidelines for children with sickle cell disease.					
d. I do not feel comfortable discussing risks and benefits of transcranial Doppler ultrasonography with my patients and their families.					
e. Guidelines for transcranial Doppler ultrasonography for children with sickle cell disease are based on questionable scientific evidence.					
f. There are conflicting guidelines regarding transcranial Doppler ultrasonography for children with sickle cell disease.					
g. Transcranial Doppler ultrasonography results predict stroke risk.					
h. Regular transcranial Doppler ultrasonography will not decrease the incidence of stroke among children with sickle cell disease.					
i. I am confident in my ability to reduce the risk of stroke in my patients with sickle cell disease.					

Statement	1 Strongly Disagree	2 Disagree	3 Neutral	4 Agree	5 Strongly Agree
j. I will not recommend chronic exchange transfusion regardless of transcranial Doppler ultrasonography results.					
k. Chronic exchange transfusion is effective at reducing stroke risk among children with sickle cell disease.					
l. Hydroxyurea is effective at reducing stroke risk among children with sickle cell disease.					
m. I am comfortable discussing the risks and benefits of chronic exchange transfusion with my patients and their families.					

6. Regardless of if you make transcranial Doppler ultrasonography recommendations, do you believe pediatric patients with sickle cell disease should receive transcranial Doppler screenings?

☐ Yes ☐ No → Skip to question 13

7. Do you currently recommend transcranial Doppler ultrasonography for your pediatric patients with sickle cell disease?

☐ Yes ☐ No; please explain: _____

8. *The following statements ask about your perspectives regarding potential barriers to your patients receiving transcranial Doppler ultrasonography. Rate your agreement with each statement from strongly disagree to strongly agree by checking the box that corresponds to your answer.*

Statement	1 Strongly Disagree	2 Disagree	3 Neutral	4 Agree	5 Strongly Agree
a. Distance from patients' homes to vascular laboratories is a barrier to receipt of transcranial Doppler ultrasonography.					
b. Authorization from private insurance carriers is a barrier to receipt of transcranial Doppler ultrasonography.					
c. Authorization from Medicaid is a barrier to receipt of transcranial Doppler ultrasonography.					
d. Lack of time/resources to describe risks and benefits to my patients and families is a barrier to receipt of transcranial Doppler ultrasonography.					
e. Parental refusal is a barrier to receipt of transcranial Doppler ultrasonography.					
f. Reimbursement from private insurance carriers is a barrier to receipt of transcranial Doppler ultrasonography.					
g. Reimbursement from Medicaid is a barrier to receipt of transcranial Doppler ultrasonography.					
h. Lack of appropriate staff to interpret results is a barrier to receipt of transcranial Doppler screening.					
i. Low patient adherence to appointments is a barrier to receipt of transcranial Doppler screening.					
j. Lack of insurance is a barrier to receipt of transcranial Doppler screening.					
k. Lack of parental belief that their child is at an increased risk for stroke is a barrier to receipt of transcranial Doppler screening.					

9. For which of the following subtypes of sickle cell disease do you or would you recommend transcranial Doppler ultrasonography? Check all that apply.

☐ Sickle cell disease - SS ☐ Sickle Cell Disease – SC ☐ Sickle Cell Trait

☐ Sickle cell disease – S β^0 thalassemia ☐ Sickle cell disease – S β^+ thalassemia

10. At what age (in years) do you or would you begin recommending transcranial Doppler ultrasonography for children with sickle cell disease who have never had a stroke? _____

11. At what age (in years) do you or would you stop recommending transcranial Doppler ultrasonography for children with sickle cell disease who have never had a stroke? _____

12. *The following actions are possible next steps after receiving the results of a FIRST transcranial Doppler ultrasonography for a child with sickle cell disease. Check which action(s) you would take for a FIRST transcranial Doppler ultrasonography result in the ranges listed at the top (normal, conditional, abnormal). Check all that apply.*

Action	1 Normal (<170 cm/sec)	2 Conditional (170–200 cm/sec)	3 Abnormal (>200 cm/sec)
a. Perform additional tests such as MRI / MRA.			
b. Repeat ultrasonography within 4-6 weeks.			
c. Repeat ultrasonography in 2-6 months.			
d. Repeat ultrasonography in 7-12 months.			
e. Recommend chronic exchange transfusion.			
f. Prescribe hydroxyurea to patient.			
g. Recommend Asprin.			
h. Do not repeat ultrasonography within 12 months; continue observation.			

13. What is your sex? ☐ Male ☐ Female

14. Which of the following best describes your race?

☐ White ☐ Black or African American ☐ Asian or Pacific Islander

☐ American Indian or Alaskan Native ☐ Other (specify): _____

15. Which of the following best describes your ethnicity? ☐ Not of Hispanic origin ☐ Hispanic origin

16. What is your age (years)? _____

17. How many years have you been in practice? _____

18. What is your specialty?

☐ Pediatrics ☐ Family Medicine ☐ Pediatric Neurology

☐ Pediatric Hematology ☐ Other (specify): _____

19. How many hours do you spend on continuing medical education per month?

☐ Less than 1 hour ☐ 1 to 5 hours ☐ More than 5 hours

20. Approximately what proportion of your pediatric patients are children with sickle cell disease?

☐ Less than 5% ☐ 5-10% ☐ 11-20% ☐ Greater than 20%

21. Approximately what proportion of your pediatric patients are covered by Medicaid?

☐ Less than 5% ☐ 5% to less than 25% ☐ 25% to less than 50% ☐ 50% or more

22. What is the ownership/affiliation of your primary practice setting?

☐ Private, independent office ☐ University / hospital / medical center (excluding sickle cell centers)

☐ Practice Network (includes HMOs) ☐ Sickle cell center / clinic

23. Approximately how many different pediatric patients do you see in a year?

☐ 1-500 ☐ 501-1,500 ☐ 1,501-3,000 ☐ Greater than 3,000

Chapter 5

Discussion

5.1 Overall Summary of Research and Finding

This dissertation investigated factors that may be influencing the low rates of TCD screening among children with SCD in the Michigan Medicaid population on multiple levels (individual, neighborhood and provider). Identification of these factors could inform the utility of targeted interventions aimed at increasing TCD screening rates.

Chapter 2 investigated overall rates of TCD screening and the frequency and predictors of missed opportunities for screening. Using Michigan Medicaid administrative data, we showed that TCD screening rates were low, particularly among adolescents ages 12 to 16. Low rates coupled with high healthcare utilization led to a high frequency of missed opportunities for TCD screening, defined as having an SCD-related healthcare encounter but no receipt of TCD screening within the same year. Increasing age was associated with increased odds for a missed opportunity, while more than 4 outpatient visits and previous receipt of TCD screening decreased the odds for a missed opportunity compared with children with 0-1 outpatient visits and children with no previous receipt of screening. Other types of SCD-related healthcare utilization, SCD comorbidities, and other demographics were not associated with a missed

opportunity. Because neighborhood factors may also play a role in receipt of TCD screening beyond the individual-level factors investigated in Chapter 2, we considered the association between various measures of neighborhood socio-demographic status identified from the American Community Survey and receipt of TCD screening among children in Wayne County, Michigan in Chapter 3. No associations were found between the socio-demographic characteristics of the neighborhoods and receipt of TCD screening, nor was any spatial pattern of TCD screening rates across the neighborhoods identified. Chapter 4 focused on factors that may influence physician adherence to TCD screening guidelines, such as physician awareness, attitudes and knowledge of guidelines, along with physician-perceived barriers to screening. These factors were explored in a mailed survey to pediatric hematologists, pediatric neurologists and PCPs treating children with SCD. Although the majority of physicians believed that children with SCD should receive TCD screening and recommended it to their patients, significant differences existed in awareness, attitudes and knowledge of TCD screening guidelines among specialties. Knowledge of specific TCD recommendations was especially low for all physicians. Distance from home to a vascular laboratory and patient adherence to appointments were identified by physicians as barriers to screening. The culmination of this work suggests that future studies are necessary to identify factors associated with TCD screening among children with SCD, allowing the design of interventions to increase screening and avert the consequences of stroke in this high-risk population.

5.2 Aims 1 and 2

Chapters 2 and 3 examined variables on both the individual and neighborhood level that may affect TCD screening rates among children with SCD in Michigan Medicaid. Receipt of TCD screening was low in each year from 2007 to 2011 (10 to 31%). TCD screening rates increased by 21% over a 5 year period, and younger children were more likely to receive screening than teenagers. SCD-related healthcare utilization was high and relatively constant over the study period; on average, children had 3 outpatient, 1 inpatient and less than 1 ED visit yearly. Given the low TCD screening rates and numerous SCD-related healthcare encounters, the frequency of missed opportunities for TCD screening was high each year, ranging from 64% to 89%. If all missed opportunities were eliminated, TCD screening rates could more than triple. We then explored potential correlates for missed opportunities, which included SCD-related healthcare utilization, SCD comorbidities and demographics. Increasing age was associated with presence of a missed opportunity (OR 1.11, CI 1.06, 1.15). This may be due to lack of physician recommendation for older children for reasons such as belief that stroke risk declines enough past age 10 as to not require TCD screening,[103] or less interaction with the healthcare system for adolescents. Children with previous receipt of TCD screening were less likely to have a missed opportunity than those without a previous screening (OR 0.23, CI 0.15, 0.38), perhaps attributable to repeat recommendations from the same physician, parental recognition of the need for screening, or clinic-specific policies conducive to receipt of TCD screening. Children with 4 to 5 (OR 0.44, CI 0.23, 0.83) or 6 or more (OR 0.25, CI 0.13, 0.49) outpatient visits compared to children with 0-1 outpatient visits were also less likely to have a missed opportunity; these children may be screened more frequently due to more

opportunities to recommend while interacting with the healthcare system. Presence of a missed opportunity was not associated with any other SCD-related healthcare utilization (i.e. ED, inpatient, hematologist visits), SCD comorbidities (i.e. hypertension, pneumococcal infection, severity of disease) or demographics (i.e. sex, sickle cell subtype), indicating that these children are not any less likely to have a missed opportunity than children without these types of healthcare encounters. Although these were not significant relationships, intervention potential exists to reduce missed opportunities through these encounters.

TCD screening rates were similarly low among children with SCD when examined in Wayne County, Michigan (7 to 36%), the home of the majority of children with SCD in Michigan. The neighborhoods where children with SCD lived had high levels of socioeconomic disadvantage and low census tract-level TCD screening rates, but no spatial pattern of TCD screening rates was identified across the county. Additionally, no association was found between the socio-demographic neighborhood factors of median household income, proportion of residents with less than high school education, proportion unemployed, or proportion African American residents and receipt of TCD screening. The lack of an association between receipt of TCD screening and neighborhood-level factors may be due to low levels of screening across all neighborhoods, along with high levels of neighborhood disadvantage and little variation in these factors between neighborhoods.

Similar to ours, numerous studies have indicated that TCD screening rates are low and children do not receive 1 TCD screening per year as recommended by the NHLBI[25,41] In a comprehensive sickle cell center (CSCCs) in Tennessee, 45% of

children with SCD were screened yearly from 2004-2006.[42] Rates in a large healthcare plan were even lower, with 11.4 screens per 100 person-years from 1999-2005; although rates reached as high as 40 screens per 100 person-years in 2002.[41] Other CSCCs have reported higher rates after initiation of TCD screening programs within the center;[43,45,55] however, even after implementation of a screening program in Philadelphia, children only averaged 3.3 screenings over an 8 year period, falling short of NHLBI guidelines.[43] Rates of TCD screening have also been increasing over time in both a large managed healthcare plan and in CSCCs, especially when comparing rates of screening before and after the STOP trial.[41,42,45] Our results reflect a similar pattern, but are for a later time period than previous studies, providing more recent information on the state of TCD screening.

Although no other study has investigated missed opportunities for TCD screening as an outcome, a few have considered predictors of TCD screening. For example, TCD screening at a CSCC has been associated with outpatient visits; however, the association was for children with more than 1 outpatient visit in a year and our results were not significant until children reached at least 4 outpatient visits in a year.[45] Another CSCC indicated previous receipt of TCD screening was associated with future receipt of screening, and younger children were more likely to receive TCD screening than older children, similar to our conclusions with missed opportunities.[41-43] Further, existing studies have reported null associations between neighborhood-level median household income, hypertension, SCD severity, sex, and hematology visits and receipt of TCD screening.[41,42,45] Our work extended the results of these studies by investigating the association of these factors with presence of a missed opportunity. Further, we

examined additional neighborhood socio-demographic factors in regard to receipt of TCD screening.

These aims advance our knowledge regarding receipt of TCD screening among children with SCD. First, the study population is a more accurate representation of the population of children with SCD than previous studies, and hence our estimates of TCD screening are less likely to be biased. This is the first study of TCD screening using the gold standard of newborn screening records to identify children with SCD. Previous studies of TCD screening have relied on inpatient and outpatient SCD-related administrative claims[41,45] or medical records from a CSCC to identify children with SCD.[42,43,55] Including only children with SCD-related healthcare encounters or who are seen at a CSCC may introduce selection bias, as we found that a considerable proportion (12 to 16%) of SCD children had no SCD-related health encounters each year. These children may be less likely to receive TCD screening due to underutilization of healthcare. Indeed, our results show lower rates of screening compared to recent studies in CSCCs, which may be a more accurate representation of the true TCD screening rates in the population of children with SCD.[42,45]

Secondly, investigation of missed opportunities for TCD screening is a novel approach to identifying potential intervention targets to increase TCD screening rates. Children with missed opportunities have contact with the healthcare system and taking advantage of these encounters may provide an appropriate time to initiate screening. Missed opportunities for TCD screening have not been enumerated in the population of children with SCD. Other studies have focused on the proportion of children receiving screening after a visit to a hematologist;[42] however, we consider a missed opportunity to

be any SCD-related healthcare encounter without a TCD screening. These encounters may signify additional opportunities to initiate screening within the healthcare system beyond merely hematologist or CSCC visits. Our results suggest that some children may be at higher risk than others for a missed opportunity, such as older children, children that have not received a screening in the past, and children without numerous outpatient visits. Interventions aimed at reducing missed opportunities among these children may be the most successful avenue to increase screening rates among children interacting with the healthcare system. Providers may also play a role in the initiation of TCD screening during these healthcare encounters, but their role in the recommendation of TCD screening is poorly understood (see Aim 3, section 5.3).

To date, no study has investigated neighborhood socio-demographic characteristics as predictors of receipt of TCD screening beyond median household income. Neighborhood of residence may be a determinant of TCD screening as it could impact access to resources and levels of social support and stress.[74-77] Neighborhood socioeconomic status has been shown to be related to all of these constructs; therefore, we investigated neighborhood socioeconomic factors (i.e. proportion unemployed, proportion less than high school education, and median household income) in relation to receipt of TCD screening. In addition, we considered proportion African American residents within a neighborhood to be a potential predictor of receipt of screening, as utilization of preventive services has been shown to be related to the racial and ethnic composition of the neighborhood.[78] Although studies have indicated that neighborhood level median household income is not associated with the receipt of TCD screening, these studies have only investigated children at CSCC, which as previously stated may

have led to selection bias.[42,45] Further, zip code level median household income was used as a proxy for individual-level socioeconomic status in predicting receipt of TCD screening. Use of smaller units (i.e., census tracts) as done in our current research may be a more accurate reflection of the neighborhood 's socioeconomic status.[79] Although we expected to find associations between neighborhood socio-demographic factors and receipt of TCD screening, none were found. This may be attributable to the low rates of screening and high levels of disadvantage in the Wayne County census tracts. It may otherwise indicate that we did not capture the neighborhood constructs that may be most relevant to TCD screening (see future directions, section 5.5).

5.3 Aim 3

Chapter 4 explored physicians' awareness, attitudes and knowledge of TCD screening guidelines for children with SCD. These internal barriers may affect the degree of physician adherence to TCD screening and therefore, influence both TCD screening rates and the frequency of missed opportunities among children with SCD. Physician-perceived external barriers to TCD screening were also identified.

The majority of physicians were familiar with national guidelines regarding TCD screening; however, one-third did indicate that they felt unfamiliar with guidelines, particularly PCPs. Physicians indicated a wide variety of guidelines would be referenced when more information was needed; the majority would reference the American Academy of Pediatrics guidelines.[39] Attitudes regarding screening differed across statements and specialties. Most physicians felt comfortable caring for children with SCD, felt that children were at a high risk of stroke, and had a positive perception of

guidelines; however, the majority of PCPs did not feel well informed regarding the guidelines, unlike pediatric hematologists and neurologists who in general, felt well informed. Self-efficacy was also lower among PCPs, with this specialty feeling uncomfortable discussing risks and benefits of TCD screening and chronic blood transfusions, along with their ability to reduce stroke risk in these children. Although pediatric hematologists scored consistently higher than pediatric neurologists and PCPs in specific knowledge questions regarding TCD screening based on NHLBI guidelines,[25] the proportion of correct was low across all specialties, with the highest proportion correct of any question being 35% (age to begin screening). Additionally, physician-perceived external barriers to TCD screening included distance from a child's home to a vascular laboratory and patient adherence to appointments, despite the fact that patient adherence has been shown to be relatively high in a CSSC and missed opportunities for screening are numerous.[42]

This aim contributes to the literature by being the first study to investigate physician internal and external barriers that may influence TCD screening across physician specialties. While our results confirm findings that hematologists identify patient adherence to appointments and distance to a vascular laboratory as external barriers to TCD screening, no study has included PCPs and pediatric neurologists.[47] The inclusion of pediatric neurologists is advantageous, as children may be referred to this specialty after an abnormal TCD screening result. PCPs may be the primary physicians seeing children that do not have regular contact with a hematologist; therefore, this contact may be the only opportunity in which TCD could be recommended for a child. We also included previously unexplored internal barriers to

adherence to screening in the survey (i.e. physician awareness, attitudes and knowledge of TCD screening guidelines) as the previous study included only physician-perceived external barriers.[47] An understanding of the multiple dimensions that may affect physician adherence to guidelines can inform the development of more appropriate interventions to increase physician recommendation of screening, as barriers to physician adherence are likely to be multifaceted.[95] In light of our results, specialty-specific educational interventions may reduce barriers to physician recommendation of TCD screening through increasing self-efficacy, outcome expectancy and knowledge of specific TCD screening guidelines. Substantial room for improvement exists across all specialties, indicating that physician barriers may be one aspect affecting the low TCD screening rates among children with SCD.

5.4 Strengths and Limitations

Overall, this dissertation investigated previously unexplored dimensions that may be contributing to low rates of TCD screening: missed opportunities, individual and neighborhood-level factors, and potential barriers to physician adherence to TCD screening guidelines. These multiple levels of influence represent a novel and more comprehensive approach to investigating factors that could potentially impact receipt of TCD screening among children with SCD than previous work.

Identification of children with SCD using Newborn Screening records in Aims 1 and 2 is a novel approach as we did not have to rely on children with SCD-related health encounters to identify our study population. Cases of SCD included in our study have been confirmed through an extensive process including the MDCH and the Sickle

Cell Disease Association of America (SCDAA) Michigan Chapter, and we can assume no false positives exist in the identified population of children with SCD used in Aims 1 and 2.[59,104] For both of these analyses, the requirement of continuous enrollment with no other forms of health insurance for the study period is also advantageous, as it allows for full capture of all healthcare claims for the child. Theoretically, this would prevent misclassification of the outcome as we did not miss claims filed with another insurance company. In addition, lack of health insurance should not prevent receipt of care in this population. The longitudinal nature of the data adds strength, as we accounted for the temporal relationship between potential correlates and the presence of a missed opportunity. Multiple years of data also allowed several observations per child, resulting in an increased sample size and more power to detect associations compared to using children as the unit of analysis.

Aim 3 is unique as it is the first study to include the subspecialties of pediatric neurology and PCPs in a physician survey regarding TCD, along with investigation of physician awareness, attitudes and knowledge of guidelines. The framework informing the development of the survey was based off results from previous studies investigating physician adherence to guidelines.[95,105] The survey considered a variety of barriers that may be influencing adherence, recognizing that physician recommendation for screening has multiple determinants. This framework and survey may be useful in other disciplines to determine which approach may be most successful to increase adherence to guidelines among physicians. Also, limiting responses to physicians currently treating children with SCD generated more appropriate results to inform interventions as

opposed to the population of physicians in general, many of which have no contact with children with SCD.

There are limitations to each aim of this dissertation. Both aims 1 and 2 had similar concerns based off the use of administrative data to identify receipt of TCD screening. TCD screening could be miscoded in Medicaid or healthcare providers may not have submitted a claim for TCD screening to Medicaid given the low level of reimbursement. Both of these circumstances would have led to an under capture of receipt of TCD screening, and led to our results showing lower screening rates than the true rate in the population of children with SCD. Along similar lines for Aim 1, administrative claims data were used for identification of SCD-related healthcare and also for potential correlates of missed opportunities. If these claims were reported incorrectly, selection bias through improper exclusion from the study population with no SCD-related healthcare encounter or information bias regarding classification of the correlates could have occurred. Although use of newborn screening to identify cases of SCD is a major strength of aims 1 and 2, newborn screening may not have captured all cases of SCD, as children may have moved into Michigan and not been captured in Michigan Newborn Screening records. In aim 1, there may be other individual-level factors influencing TCD screening that were not included, such as pain crises, history of stroke within the family, and maternal education.[41,45] There also may have been additional neighborhood level factors influencing the receipt of TCD screening, such as lack of public transportation services, availability of medical services or neighborhood safety and disorder. Our results from aims 1 and 2 may not be generalizable to the rest of the United States, as we only investigated TCD screening among children in

Michigan Medicaid. The presence of the SCDAA is strong in Michigan, and may affect healthcare such as receipt of TCD screening or care at a CSCC. Further, these aims may have been underpowered to find associations with the individual- and neighborhood-level predictors. The study design did not allow inclusion of a specific number of children (i.e. no formal sample size was determined); instead, every eligible child was included that could be identified from 2007-2011. Selection bias may be present, as children with SCD have higher mortality than children without SCD; however, mortality has declined in the past decades with approximately 94% of children with HbSS surviving until the age of 18 years.[106]

Additional limitations exist specifically for aims 1 and 2. The definition of missed opportunities in Aim 1 cast a wide net, including all SCD-related healthcare encounters with no TCD screening as a missed opportunity. This may overstate true missed opportunities; for example, children in the ED may not be an appropriate target for reduction of missed opportunities, particularly if the primary reason for the visit was not SCD. Although the presence of a missed opportunity was identified, there are no indications in administrative claims behind the reason for the missed opportunity. It is unknown what course of events led to the lack of TCD screening, as it could be lack of physician recommendation, physician recommendation but no appointment scheduled, parental refusal, or any host of other situations. Limitations of aim 2 include use of census tracts to define neighborhoods as this may not be the most appropriate boundaries to reflect the true neighborhood the child/family interacts with and use of the urban area of Wayne County only. Although the majority of children with SCD in Michigan reside in Wayne County, other states have significant populations of children

with SCD in rural areas.[107] Area-level factors influencing TCD screening may differ substantially between rural and urban areas; however, the population of children with SCD in Michigan is not an appropriate population to use in evaluation of these differences. A further limitation to Aim 2 is the use of the child's address on January 1 of each year to determine residence. Children with SCD have high mobility which may have resulted in inappropriate inclusion or exclusion in the study population based on their address or assignment to the incorrect neighborhood within Wayne County.

For Aim 3, the sample size of physicians was limited due to cost restraints, and the response rate of 44% was low. This response rate however is in line with other physician surveys and is higher than the response rate of 20% for the survey of US hematologists in regard to TCD screening.[47,100-102] The low response rate may be a problem if the physicians that responded had different awareness, attitudes or knowledge of guidelines as compared to physicians that did not answer the survey. Additionally, the survey was based on self-report, which may introduce bias in the results. The use of PCPs in Michigan only was necessary since they were identified using Michigan Medicaid claims data; however, the PCP responses may not be generalizable outside of Michigan, or even to the population of PCPs in Michigan if response bias is present. A further limitation to note with Aim 3 is that although factors that may influence adherence to guidelines were identified, no information regarding the actual adherence to guidelines among physicians was available. Therefore, more information is necessary to determine if these factors are truly influencing TCD screening rates.

5.5 Future Directions

Future studies could expand upon the results in this dissertation in two ways: 1) additional work addressing methodological considerations, and 2) continued focus on the multiple dimensions of influence on TCD screening, including neighborhoods, physicians, caregivers and clinics. Additional implications of potential harmonization of guidelines and the Affordable Care Act should also be considered.

Methodological Considerations

Additional methodological work could be conducted to 1) investigate the accuracy of TCD screening as identified through administrative claims and 2) identify methods to classify children with SCD when newborn screening information is not available. The accuracy of administrative claims in identification of TCD screening would require abstraction of medical records for a sample of children with SCD with available claims data. If a proportion of screens are not being detected by administrative claims data, rates may be higher than reported and would suggest different methods are needed to study TCD screening. All states may not have the capacity to perform the linkages necessary between Newborn Screening and Medicaid as done in the current research; however, alternative strategies are being developed to accurately identify children with SCD. These methods use Michigan Medicaid administrative claims data for SCD and compare combinations of these claims to the recognized gold standard of newborn screening results to determine their sensitivity and specificity in identifying children with SCD. Similar methods have been developed for use in quality assessment studies of other pediatric conditions, such as asthma and diabetes.[108-112] This method will also allow children without a newborn screening result to be included in the study

population in states that are able to perform linkages; for example, children born in another state but residing in Michigan. As our study also focused exclusively on children enrolled in Michigan Medicaid, other sources of information could increase the number of subjects besides those listed above. For example, children with SCD enrolled in private insurance could be identified using administrative claims. This could potentially increase our sample size by 30-45%. Including these children may be a more accurate reflection of TCD screening rates in the total population of children with SCD as opposed to the rates among children enrolled in Medicaid. After these issues have been addressed, additional study is needed to understand the true rates of TCD screening in a broader population of children with SCD than has been previously explored.[42,43,45,55]

With a more firm methodological grounding of the accuracy of identification of TCD screening rates in a broader population, missed opportunities across other states and in other populations could be considered. As each child with SCD interacts with the healthcare system, reduction of missed opportunities provides a unique circumstance to increase TCD screening rates. An understanding of the frequency missed opportunities and their predictors would help identify children at high-risk for a missed opportunity. This approach has been successful in interventions aimed at increasing immunization rates among children.[53,54] Missed opportunities could occur through multiple pathways, such as lack of physician recommendation, parental refusal to receive screening, or lack of patient adherence to screening appointments.[41,42,46,47] These situations require different intervention approaches to reduce missed opportunities; therefore, elucidation of these situations through the use of medical records and interviews with caregivers may be key in intervention development. Identification of the reasons behind missed

opportunities can lead to the development of targeted interventions to reduce their likelihood. Although children that do not have missed opportunity but also do not receive TCD screening are also important targets for increasing TCD screening rates, a different methodological approach is necessary to study this population. Also, an intervention approach that does not rely on healthcare utilization to initiate screening would be necessary for these children.

Multiple dimensions of Influence on TCD Screening

Neighborhood Factors

In recent years, epidemiology has recognized the importance of factors impacting health on multiple levels as opposed to merely individual-based explanations.[113] Understanding the social and physical environment in which a person belongs has become an area of focus, with neighborhoods being particularly relevant in many contexts.[113-116] Although we did not identify any neighborhood-level factors associated with the receipt of TCD screening or any spatial pattern in TCD screening rates across neighborhoods, this may be attributable to the low rates of screening and high levels of disadvantage across the Wayne County census tracts. Investigation of socio-demographic characteristics across neighborhoods showing more variation in neighborhood-level TCD screening rates and characteristics may identify potential factors associated with screening rates. Additional unmeasured neighborhood factors may be influencing rates and could be considered in future studies, such as neighborhood safety and disorder, public transportation, and accessibility of medical resources. Lack of neighborhood safety and neighborhood disorder have been associated with poor health outcomes and may affect receipt of TCD screening.[117]

Furthermore, lack of public transportation in a neighborhood may affect TCD screening through limiting the accessibility of a CSCC. Rates of TCD screening are higher in CSCC with TCD screening programs than in children enrolled in healthcare plans or in our study population, indicating children with the ability to utilize a CSCC may be more likely to receive TCD screening.[42,45,55] These factors have been assessed in other studies outside of SCD using standardized scales in interviews, along with non-interview methods such as videotaped assessments of the neighborhood and use of Google Maps to assess neighborhood features.[118-120] Assessment of the neighborhoods using these methods, along with utilization of administrative claims to identify receipt of TCD screening, could begin to explore the relationships between neighborhoods and receipt of TCD screening using more refined measures. If neighborhood factors associated with TCD screening could be identified, it may be possible to develop more cost and resource effective interventions targeting specific neighborhoods to raise TCD screening rates, as opposed to a more general intervention to raise TCD screening rates across all children with SCD.

Physician Factors

Aim 3 identified factors that may influence physician adherence to receipt of TCD screening, along with potential barriers to receipt of screening; however, the impact of these factors in relation to actual adherence to screening is unknown. One study investigated physician adherence to clinic-specific TCD recommendation guidelines; however, this was only among hematologists at a CSCC.[42] Medical records could be used to identify physician recommendation of TCD screening. Then, physician awareness, attitudes and knowledge of TCD screening could be tied to the physician's

recommendation practices to identify which barriers are related to lack of adherence. It is important to identify which barriers exist for recommendation of TCD screening guidelines so interventions to increase physician adherence to TCD screening guidelines can be correctly targeted.[95,105] Targeting specific physician-level factors influencing screening recommendations by physicians would be a cost and resource-effective method to impact screening rates.

Caregiver Factors

Caregivers may play an important role in the process of receipt of TCD screening, and further studies are necessary to clarify the perceptions of the caregiver regarding TCD screening. Although one study has investigated caregiver perceptions of TCD screening, the sample size was small and the population from one clinic.[46] Studies should be conducted which include a larger number of caregivers identified through many different resources, and should investigate factors such as self-efficacy, awareness, outcome expectancy and attitudes toward TCD screening to identify the role of the caregiver in the receipt of TCD screening to inform appropriate educational interventions for caregivers.

Clinic Factors

Identification of additional intervention targets may involve investigation of the clinical roadmap of the process in which a child receives TCD screening within clinics. This process is not well understood and varies substantially across institutions.[42,45,55] For example, rates of TCD screening have risen substantially when a dedicated nurse is in charge of the TCD screening program.[55] Also, time between recommendation of TCD screening and receipt of screening may be another avenue to investigate within the

roadmap. Children with the opportunity to receive screening at the same time as the recommendation may be more likely to be screened than children with a separate future appointment for TCD screening only.[55] Previous studies have shown success at increasing TCD screening rates through clinic-based methods such as a dedicated individual to follow up on TCD screening, offering TCD screening on-site, and sending reminders.[42,55] Identification of clinic barriers to TCD screening may allow for a restructuring of the hospital or clinic level policy to reflect the most likely process for children to receive screening when recommended.

Harmonization of Guidelines

TCD screening guidelines differ substantially across multiple national organizations. As we showed that physicians reference many different guidelines for information regarding TCD screening, harmonization of these guidelines could potentially increase TCD screening rates. Development of a national advisory committee would be appropriate to spearhead this effort. Precedent for such a strategy has been set by the Advisory Committee on Immunization Practices (ACIP). In 1995, the ACIP began releasing yearly harmonized guidelines for childhood immunization schedules. Prior to the yearly release, the ACIP published vaccine recommendations periodically. A study comparing rates of morbidity and mortality from before and after implementation of national recommendations for vaccine preventable diseases (VPD) showed 80% reduction of cases and deaths of most diseases targeted since 1980.[121] Given the substantial success of the implementation of national guidelines by an advisory committee, development of a similar organization within SCD may be

advantageous in increasing not only TCD screening, but the quality and consistency of care for children with SCD.

Policy Implications

Implementation of the Affordable Care Act (ACA) may provide additional opportunities to increase TCD screening through additional funding for community health centers and PCPs in medically underserved areas. In 2012, community health centers treated 21 million people, the majority of which (62%) were minorities. Additionally, 32% of patients were children.[122] These centers are generally located in underserved and low-income communities, such as the city of Detroit. The ACA provides $11 billion over a 5 year period for the expansion of these health centers across the US.[122] Although all children in this study were covered by health insurance, the expansion of health centers could increase TCD screening through reduction of missed opportunities by increasing interactions with the healthcare system. Additionally, expansion of community health centers may increase the likelihood of the child having a medical home due to their emphasis on coordinated and comprehensive care.[123] Children greatly benefit from having a medical home, as it is associated with fewer unmet health needs and less delayed care, along with increased receipt of preventive care, particularly among children with special health care needs.[124-126] Community health centers also may reduce other barriers to access to care by providing expanded hours, increased convenience of location, and decreased language barriers. Furthermore, the ACA aims to increase PCPs working in underserved areas similar to Detroit.[127] Increased availability of PCPs may increase the likelihood of having a medical home and receiving preventive services.[128] However, we did show that PCPs

have low knowledge, self-efficacy and outcome expectancy regarding TCD screening. As PCPs may have consistent contact with children with SCD, particularly in these areas, educational interventions regarding the importance of TCD screening, and the specific guidelines regarding TCD screening, may be integral to increase TCD screening rates among this minority, low-income population.

An additional way in which policy could affect TCD screening is through meaningful use criteria. Meaningful use criteria were developed by the Centers for Medicare and Medicaid (CMS) Incentives program. It is the set of standards used to measure use of electronic health records (EHR) to allow incentive based payments to physicians. Measures of meaningful use include quality measures to improve outcomes, processes and systems. Increased use of EHR in concordance with the meaningful use criteria may be able to systematically increase TCD screening rates through accurate reporting of previous receipt, built-in reminders for upcoming appointments, and improvements in the efficiency of the clinical roadmap in which the child receives a TCD screening.

5.6 Conclusion

This dissertation addresses factors that may influence TCD screening rates among children with SCD. The results indicate that TCD screening rates remain low and there is substantial room for improvement through reduction of both missed opportunities and barriers to physician adherence to TCD screening guidelines. Further investigation of neighborhood-level factors may also identify additional targets for improvement. The results of this research, along with additional robust and expanded research in this area, may inform interventions at the individual, neighborhood, provider,

caregiver, and hospital/clinic level that address the receipt of TCD screening. Ultimately, these interventions may increase TCD screening among children with SCD and reduce the incidence of stroke in this high-risk population.

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