ASSESSMENT OF HEMOGLOBINOPATHY TRAIT NOTIFICATION IN WESTERN PENNSYLVANIA NEWBORN SCREENING

by

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BA, Biochemistry, Swarthmore College, 2011

Submitted to the Graduate Faculty of

the Department of Human Genetics

Graduate School of Public Health in partial fulfillment

of the requirements for the degrees of

Master of Science and Master of Public Health

University of Pittsburgh

2019

UNIVERSITY OF PITTSBURGH

GRADUATE SCHOOL OF PUBLIC HEALTH

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ABSTRACT

Background: Newborn Screening (NBS) is a state-run public health program, which screens infants at birth for congenital conditions that may cause significant disability or death without prompt intervention. Carriers of sickle cell disease (SCD) are incidentally identified in the screening process yet are generally considered to be healthy. States' policies regarding the incidental finding vary. Sharing the result challenges the traditional scope of NBS, and the history of sickle cell screening in the United States cautions against the program's potential harms. States' programs that do disclose positive sickle cell trait (SCT) status are primarily motivated by its reproductive implications. These programs notify stakeholders through a variety of means. This study sought to evaluate the impact of SCT notification on families in Pennsylvania, who are informed via a mailed letter.

Methods: Parents in Western Pennsylvania who received the SCT notification letter within the past year were surveyed regarding their understanding of SCD, anxiety related to the notification, and anticipated sharing of the health information.

Results: Ninety-four of 434 notified families completed the survey by mail and telephone. Over 36% of respondents were unclear of the inheritance pattern of SCD, and 29% incorrectly answered that SCT could develop into SCD. The greatest misunderstanding was found regarding Hemoglobin C trait and specific reproductive risks. The letter elicited anxiety in approximately

one-third of parents. Over 90% of respondents planned to discuss the letter with their partner, their infant's primary care provider, and their infant at an older age.

Conclusions: The current notification letter inadequately conveys the health and reproductive implications of SCT and may contribute to anxiety in a meaningful proportion of parents. These findings support the utility of follow-up services in promoting understanding and minimizing stress related to carrier identification through NBS. Parents appear to appreciate the relevance of the information, based on their intent to share it with appropriate family and healthcare providers. Further research is needed to clarify additional effects of the program, in particular for the infant, who should be a primary beneficiary of NBS.

Public Health Significance: This study may inform policies regarding disclosure of SCT status through NBS.

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PREFACE

I would like to extend my sincerest gratitude to my committee chair, Dr. Cheryl Hillery, and to my committee members, Andrea Durst and Elena Kessler, for lending their expertise and guidance to this project. It has been such a privilege to work with and learn from all three. I must also express my deepest appreciation to my program directors, Robin Grubs and Andrea Durst. Their wisdom and unparalleled enthusiasm in sharing it has shaped not only this work, but the genetic counselor I aspire to be. To my peers at the Pediatric Sickle Cell Clinic and Children's Sickle Cell Foundation: Thank you for your help folding surveys, fixing printer jams, and most importantly, offering your insight and company. The value of these acts cannot be overstated. I am also extremely thankful to my classmates, who have been some of my most valuable teachers and friends throughout these two years. I hope they know that this is a lifetime appointment.

Finally, to my parents, my brother, and my partner, Luke: Thank you for your unending love and support.

1.0 INTRODUCTION

Newborn Screening (NBS) is a public health program that aims to diagnose congenital conditions in infants, so they may be provided with timely intervention.[1] Since 2006, all 50 states and the District of Columbia have screened for sickle cell disease (SCD) through NBS.[2] SCD is an autosomal recessive blood condition with multisystem pathology.[3,4] Infants and children with SCD have an increased risk of potentially fatal pneumococcal infection, and the condition's inclusion in NBS is based on the significant protection against infection that is conferred by daily penicillin started in infancy.[5,6] Heterozygous carriers of SCD experience few related health consequences.[7] However, they may have a baby with SCD if their partner also has a variant hemoglobin trait.

The heterozygote carrier state, more commonly known as having sickle cell trait (SCT), is identified incidentally when screening for SCD during NBS. States that disclose the positive screening result to families are primarily compelled to do so by the information's potential to inform reproductive decisions.[6,8] However, this health information comes prematurely for the infant. It may not be recalled at the point in life when it is relevant and threatens their autonomy to choose whether or not to undergo carrier screening. While greater reproductive benefit may come to the screened infant's parents, this is outside the traditional scope of the NBS program.[9] There is the additional concern that SCT notification may lead to adverse psychological and social harms, many of which were demonstrated in the country's earliest SCD screening programs.[10–13]

Studies of those communities most affected by SCD, which in the United States is primarily African American communities, have found that the information that trait notification seeks to provide is largely desired.[14–18] Professional clinical and prenatal guidelines pertaining to SCD also

call for greater awareness of personal trait status and of its reproductive implications.[19,20] Programs' abilities to achieve this informative benefit of SCT notification while minimizing harm may rest in their execution. Great variation exists in how programs respond to a positive screen for SCT.[21] Notification and counseling may be provided by the infant's pediatrician, a specialized healthcare provider such as a genetic counselor, or may not be provided at all. Few states actively pursue follow-up with families whose infants screen positive for SCT to ensure that they have received the information.[21]

A 2011 study performed at the Pediatric Sickle Cell Clinic of the University of Pittsburgh Medical Center (UPMC) Children's Hospital of Pittsburgh (CHP) provided evidence that genetic counseling for SCT notification is positively received by families.[22] Following genetic counseling, mothers demonstrated relatively high SCD knowledge scores, reduced anxiety, and a greater reported likelihood to share the health information with close family members. While genetic counseling is still available to those who request the service, the program for active follow-up of SCT NBS results at the Pediatric Sickle Cell Clinic of CHP, which included three calls made to the family by a specialized healthcare provider to offer genetic counseling or other educational and counseling services over the telephone or through the mail, has not been sustained. As a consequence, trait notification occurs solely through a letter and informational brochure for the majority of families. The mailing, which is sent within two weeks of the infant's positive screen, also includes contact information for the Pediatric Sickle Cell Clinic. No additional services are provided through the NBS program unless the family actively pursues them.

This study seeks to characterize the experience of families who are notified of their infant's positive NBS screen for SCT through the mail. A survey was administered to families living in Western Pennsylvania who received the notification letter for either Sickle S trait or Hemoglobin

C (HbC) trait. The Pediatric Sickle Cell Clinic of CHP is contracted with the Pennsylvania Department of Health to follow-up on positive NBS results for hemoglobinopathies and to notify families for hemoglobinopathy traits in 19 counties.[23] As this is the same region from which families were recruited for the previous studies of genetic counseling following SCT notification, this current study may inform both the understanding of how the genetic information is received through the letter alone, as well as how additional educational and counseling services may affect its impact.[22,24]

This study will focus on knowledge of SCD, the letter's emotional impact on notified parents, and disclosure patterns of the health information, as these describe three of the program's potential benefits and harms. The data generated by this study may provide insight into how positive SCT results are disclosed through the current NBS program of Pennsylvania, as well as potentially by other states' programs. We anticipate that results of this study will guide revision of the NBS trait notification letter currently sent out to families in Western Pennsylvania.

1.1 SPECIFIC AIMS

1.1.1 Specific Aim 1

To assess knowledge levels regarding the health and reproductive implications of SCD among mothers who have been notified of their infant's positive screen for Sickle S trait or HbC trait through the current NBS program of Western Pennsylvania, which consists of an informational mailing sent within two weeks of the positive screening result. Knowledge will be

measured through an eight-question true/false and multiple-choice questionnaire administered through the mail or telephone within approximately one year of the infant's birth.

1.1.2 Specific Aim 2

To determine through mail and telephone surveys whether trait notification for SCT through the mail results in increased anxiety in notified parents. The survey tools will be the PROMIS Short Form 8a Scale of Anxiety (PROMIS) for the mail surveys and a single yes/no question for the telephone surveys.

1.1.3 Specific Aim 3

To examine the willingness of parents to share their infant's SCT status with their reproductive partner, relevant healthcare providers, and the infant him or herself at an older age. This will be measured through both mail and telephone surveys, in which participants will be asked if they have shared or intend to share the letter's health information with the respective individuals.

2.0 LITERATURE REVIEW

2.1 SICKLE CELL DISEASE

Sickle cell disease (SCD) is a group of inherited blood disorders characterized by structurally abnormal hemoglobin.[3,4] The condition's name derives from the physical deformation, or sickling, of red blood cells (RBC) that may be observed on blood smears of affected individuals.[25] Sickled RBCs tend to obstruct blood flow through the vessels and have a decreased lifespan.[4] These properties of affected RBCs contribute to the pain crises, extensive organ damage, and hemolytic anemia that characterize the clinical presentation of SCD.[3,4] As one of the most common single-gene disorders, SCD represents a significant public health concern both in the United States and worldwide.[26]

2.1.1 Molecular Genetics

SCD is a monogenetic disorder that affects hemoglobin, the oxygen-transporting molecule of RBCs.[3] Hemoglobin is a tetramer composed of two unlike pairs of globin polypeptides. The polypeptides are coded for by the globin genes on chromosomes 11 and 16. Differential expression of the globin genes allows for the composition of hemoglobin to change throughout development.[27]

Fetal hemoglobin (HbF) is the predominant form of hemoglobin at birth.[27] HbF consists of two alpha subunits, encoded by the *HBA* gene pair (*HBA1* and *HBA2*), and two gamma subunits, encoded by HBG gene pair (*HBG1* and *HBG2*). During fetal development, adult hemoglobin (HbA) gradually begins to replace HbF. By six months of age, approximately 97% of the

hemoglobin in the blood of individuals not affected with SCD is HbA.[27] The HbA tetramer consists of two alpha subunits and two beta subunits. The latter are encoded by the *HBB* gene. For individuals with SCD, the transition from HbF to HbA is delayed. HbF levels also remain perpetually higher in affected individuals and range between 2% to 20%.[28]

The abnormalities in hemoglobin that define SCD arises from mutations in the *HBB* gene.[3] Causative mutations of SCD lead to either a structurally variant form of the beta globin subunit or in diminished or absent *HBB* protein product. Individuals with SCD possess at least one HbS allele, in which a thymine to adenine point mutation results in the substitution of valine for glutamic acid at the sixth amino acid of the *HBB* gene (Glu6Val).[29] This is translated into a structurally variant beta globin subunit that gives rise to a form of hemoglobin known as Hemoglobin S (HbS), or Sickle Hemoglobin. The most common form of SCD is caused by biallelic HbS alleles. This is known as HbSS disease, or sickle cell anemia.[26] In the United States, HbSS disease accounts for approximately 60 to 70% of SCD.[30]

While hundreds of hemoglobin variants have been characterized, clinical relevance is limited to a smaller subset. Common *HBB* alleles that contribute to SCD include HbC (Glu6Lys), HbD (Glu121Gln), and HbE (Glu121Lys).[31] Genotype serves as a significant predictor of clinical severity in SCD.[32] HbSS disease is typically one of the most severe forms of the condition, while HbSC disease, which is characterized by one HbC allele and one HbS allele, is typically more mild.[33] HbSC disease is the second most common form of SCD in the United States, where it accounts for between 18 to 25% of SCD.[34]

Pathogenic variants in the *HBB* gene that affect the quantity of beta globin, rather than its structure, can also contribute to SCD. Referred to as β-thalassemia mutations, these are either gene deletions or mutations that inhibit *HBB* gene transcription or mRNA stability and translation.[3] The

clinical significance of a β-thalassemia mutation is based on the degree of residual beta globin gene expression. The β^+ allele is associated with diminished protein product, whereas the β^0 allele is associated with no protein product. Accordingly, HbS-β^0 Thalassemia typically has a severe presentation like that of HbSS disease, while those with HbS-β^+ Thalassemia are typically more mildly affected.[32] HbS-$\beta^{+/0}$ Thalassemia together account for between 1 to 6% of SCD in the United States.[34]

2.1.2 Pathophysiology

The clinical features of SCD arises from the unique chemical properties of HbS. Namely, HbS polymerizes in its deoxygenated state.[3] Long, stiff protein fibers of polymerized HbS form within the RBCs. This deforms the cells from their usual donut shape into the sickle shape that is synonymous with SCD.[35] HbS polymerization lessens the integrity of the RBC cytoskeleton and cellular membrane through repeat sickling.[35] This causes the lifespan of circulating RBCs in individuals with SCD to average 20 days, as compared to the 120 day lifespan of unaffected RBCs. In some affected individuals, the sickled RBCs may circulate as few as five to seven days.[35] The shortened lifespan of RBCs in SCD results in hemolytic anemia, one of the condition's primary features.[3]

Sickled RBCs are also less elastic and more prone to adhere to one another and to other circulating cells.[4] These qualities stimulate heterocellular aggregation of the sickled RBCs with other circulating components, such as leukocytes and platelets. Blood flow through the microvasculature can be obstructed by these aggregates, as they also demonstrate greater adherence to the vascular endothelium. When the blood flow is obstruction in the microvasculature in this way, this is known as vaso-occlusion. Vaso-occlusion can lead to ischemia, infarction, and

tissue death.[35] The widespread effects of recurrent vaso-occlusion events account for many of the multisystemic manifestations of SCD.

Pain Episodes: Vaso-occlusive episodes result in ischemic tissue injury from prolonged oxygen and nutrient deprivation.[35] This is commonly experienced as acute pain. Pain crises are the hallmark clinical feature of SCD.[3] The events often come on unpredictably and may be precipitated by environmental factors, such as dehydration or hypoxia arising from physical exertion.[36] In infants, pain is most often reported in the extremities; whereas in adolescents and adults, it typically presents in the chest, abdomen, back, and head.[37] Pain episodes usually last between four to six days. In the United States, they are the primary cause of emergency room visits as well as hospital admissions related to SCD.[38] Dactylitis, or the painful swelling in the hands and feet, is another manifestation of vaso-occlusion in the extremities. This is often the first sign of SCD observed in infants.[4]

Spleen Dysfunction: The spleen is one of the earliest organs involved in SCD.[39] Splenic dysfunction appears to arise from recurrent vaso-occlusion and infarction and can lead to progressive atrophy and/or splenomegaly. By the age of five, approximately 94% of children with HbSS disease will have developed functional asplenia.[40]

Insufficient splenic filtration of sickled RBCs, bacteria, and other waste products contributes to impaired immune response.[41] Other common complications of SCD, such as impaired antibody production, tissue ischemia, and micronutrient deficiency, exacerbate immune dysfunction in affected individuals.[44] Infants and young children with SCD are particularly susceptible to invasive encapsulated bacterial infections and sepsis. Prior to the implementation of effective intervention, infection was associated with between 20%-50% of childhood deaths in

SCD in the United States.[46] Infection remains the primary cause of death for those with SCD around the world.[47–49]

Another life-threatening complication of SCD in infants and children related to the spleen is acute splenic sequestration crises (ASSC).[50] ASSC arises from rapid accumulation of sickled RBCs and other circulating blood constituents in the spleen, which results in a sudden onset of anemia and threat for hypovolemic shock.[4] Acute splenic sequestration crises commonly present with severe anemia; lethargy, irritability, abdominal pain and/or distention, and nausea may also arise. Without the timely intervention of a blood transfusion, splenic sequestration can result in death. Acute splenic sequestration is most prevalent between five months to two years of age and is the second leading cause of mortality in children with SCD.[42]

Acute Chest Syndrome: The vasculature of the lung is particularly susceptible to complications of SCD. A primary manifestation of the disorder's cardiovascular involvement is Acute Chest Syndrome (ACS). ACS is characterized by infiltration of sickled RBCs into the pulmonary vasculature.[43] It is also associated with increased white blood cell count and pneumonia-like symptoms. Often, it is preceded by a vaso-occlusion crisis, and in children, it is commonly precipitated by infection or asthma.[36] ACS presents typically presents with shortness of breath (tachypnea) and hypoxia, as well as potentially chest pain, fever, pain in the arms, legs, and sternum. It is the second most common cause for SCD-related hospitalization in adults.[36]

Neurological involvement: Vaso-occlusive events in the larger arteries of the brain can lead to ischemic strokes. Without transfusion therapy, the risk of recurrence in affected children is at least 67%.[44] Cognitive and physical impairment is a serious complication of such events. Silent cerebral infarctions, which are defined as abnormal brain magnetic resonance imaging findings in the absence of a history of neurological deficits, occur in over one-third (35%) of children with

HbSS disease.[45] These events can cause lasting brain injury. The risk for hemorrhagic strokes is also increased with SCD, with the events primarily occurring in adulthood. While more rare than ischemic strokes, hemorrhagic strokes are associated with a 24-65% mortality rate in SCD.[46]

2.1.3 Sickle Cell Trait

SCD is an autosomal recessive condition.[47] Its carrier state is commonly referred to as sickle cell trait (SCT). Approximately three million individuals in the United States are estimated to be heterozygous for the HbS allele., also known as Sickle S trait[30] In these individuals, HbS concentration in the RBCs ranges from between 20 to 45%.[48] This is sufficiently low to preclude hemoglobin polymerization under normal physiological conditions. Consequently, the RBCs of carriers of the HbS allele do not tend to undergo sickling *in vivo* and do not experience the clinical complications of SCD except under extreme sickling conditions.[35,48]

Clinical Manifestations: SCT has historically been confused as a more mild form of SCD.[10,13] However, while a number of complications have been associated with the carrier state, the great majority of individuals with SCT remain asymptomatic.[7,49] A 2018 evidence-based review by Naik et al. aimed to clarify the extent to which SCT affects health. From an initial screen of 7,083 articles published between 1970 to 2018, the review's authors evaluated 41 observational control studies for their support of an association between SCT and an increased risk for clinical outcomes in six categories.[7] The majority of studies were cohort (n = 16) and case-control (n = 16) studies.

The review found high-strength evidence for an increased risk of three complications for carriers of the HbS allele: pulmonary embolism (PE), proteinuria, and chronic kidney disease (CKD). One high-quality study of PE risk found a prevalence of 5.2% in those with SCT compared

to a prevalence of 2.5% in those without; this represents a hazard ratio (HR) of 2.24 (95% CI = 1.28 to 3.95) associated with SCT.[50] Regarding proteinuria, risk for the renal complication was found by one high-quality study to be 1.86-times higher (95% CI = 1.49 to 2.31) in African Americans with SCT compared to those without. Finally, the risk for chronic kidney disease associated with SCT was found to be 1.57 times greater (19.2% versus 13.5% prevalence) by one high-quality study and 1.89-time higher (1.59 to 2.23) by a second high-quality study.[51] The review also found an increased risk for exertional rhabdomyolysis supported by a moderate-level of evidence. For the remaining complications examined, which comprised the majority, low-strength or insufficient evidence was found in support of an association with SCT.

Exertion-related Events: A potential complication of SCT that has received much attention both medically and in the media is the risk for exertion-related injury. Extreme physical exertion may cause significant changes in pH, oxygen availability, temperature, and RBC hydration, which could potentially lead to RBC sickling and acute vaso-occlusion events in those with SCT.[52] Particularly in the setting of dehydration and hypoxemia, these metabolic changes have been postulated to contribute to potentially fatal events of rhabdomyolysis, heat illness, cardiac arrhythmia, or renal failure as a result of intense exercise or other physical exertion. Reports of sudden death owing to extreme exertion in those with SCT first appeared in 1970s and focused on sudden death in military recruits performing boot camp drills.[53,54] More recently, case reports have implicated SCT as the cause of sudden death in college and professional athletes as well.[52,53]

In their 2018 review, Naik et al. reviewed the risk for exertion-related complications, namely splenic infarction, exertional rhabdomyolysis, and sudden death associated with SCT.[7] No evidence was found to support an association of splenic infarction with SCT. Two studies were

reviewed for evidence regarding a risk of exertion-related rhabdomyolysis.[55,56] The first, a 15-subject case-control study, provided low-quality evidence in support of an increased risk owing to SCT due to its small size and lack of adjustment for confounders.[55] The second study provided moderate-quality evidence for this increased risk.[56] This 2016 study was funded by the NHLBI and Uniformed Services University of the Health Sciences and reviewed events of exertional rhabdomyolysis and death as they occurred between 2011 and 2014 among African American soldiers enlisted in the US Army. Of the 47,944 individuals, 3,564 were positive for SCT. A key strength of this study was that trait status was established in all subjects through laboratory testing, rather than self-report or medical history, ensuring validity to this variable. Three-hundred and ninety-one events of exertional rhabdomyolysis were found among the 1.61 million person-months analyzed. Forty-two events occurred among individuals positive for SCT (1.2%), compared to 349 among those without SCT (0.8%). SCT was consequently found to be associated with a significantly increased risk of exertional rhabdomyolysis, with a HR of 1.54 (p-value = 0.008).[56]

The study contextualized its results by analyzing the risk for these medical events in relation to reported characteristics besides SCT status, including body-mass index (BMI), tobacco, statin, and antipsychotic use.[56] The increased risk of rhabdomyolysis associated with SCT was nearly identical in magnitude to that associated with tobacco use (HR = 1.54, $p < 0.001$). The HR associated with SCT was also similar to that associated with having a higher BMI, defined as 30.0 or greater. Compared to a BMI less than 25.0, the HR associated with higher BMI was 1.39 ($p = 0.03$). Finally, use of statins or antipsychotic agents were found to be associated with a greater risk of rhabdomyolysis than was having SCT, with HR of 2.89 ($p = 0.001$) and 3.02 ($p = 0.008$), respectively. Overall, Naik et al. determined that moderate-quality evidence supports a higher

relative risk, yet low absolute risk, for exertion-related rhabdomyolysis associated with positive SCT status.

Lastly, Naik et al. found low-strength evidence in support of an increased risk for sudden death arising from extreme exertion in those with SCT.[7] This conclusion was drawn from consideration of two studies, both of which providing moderate quality evidence. The first was a 1987 retrospective review by Kark et al. considered to be seminal in establishing the connection between SCT and exercise-related death.[54] The study evaluated for the relative risk of sudden unexplained death among 466,300 African Americans undergoing military basic training between 1977 and 1981.[7] Using prevalence measures, the risk of sudden death among those with SCT was found to be 15-fold higher than those without (95% CI = 6 to 38). Thirteen total deaths occurred among those with SCT (0.03%), compared to ten among those who did not have SCT (0.0002%). Naik et al. found no association between SCT and "non-battle-related death" after adjusting for variables such as sex, age, rank, BMI, and smoking.[7] The second study examined by Naik et al. was the 2016 study which was also considered for rhabdomyolysis risk.[56] In this case, ninety-six deaths, battle and non-battle-related, were recorded. Seven of these deaths were among individuals with SCT (0.2%), and 89 deaths were among those without SCT (0.2%). From these mortality rates, no significant increased risk of death was found to be associated with positive SCT status (HR = 0.99, p = 0.97).

In spite of the weak connection between SCT and sudden death due to extreme exertion, multiple groups, including the United States armed forces and collegiate and professional sports associations have instigated screening programs for SCT.[57–59] In 2007, the National Athletic Trainers' Association (NATA) put forth the consensus statement "Sickle Cell Trait and The Athlete," which recommended screening and precautions for athletes with SCT, while supporting

their participation in all sports.[60] Additionally, it recommended education for both coaches and athletes regarding how to appropriately respond to the potential complications of SCT. However, the recommendations were not evidence-based and were not supported by many professional groups, including the Sickle Cell Disease Association of America, American Society of Hematology, and the Secretary's Advisory Committee Heritable Disorders in Newborn and Children (SACHDNC).[58,61,62]

While the United States' army ceased its screening program in 1996 in favor of universally applied precautions, both the Air Force and the National Collegiate Athletic Association (NCAA) continue to require screening for SCT.[59] These programs have been met with criticism for being litigious in nature, at the cost of potential stigmatization and loss of privacy for participants.[49,59] SACHDNC does not endorse the NCAA screening program. Rather, the Committee's recommendation is for all SCT screening to be performed in an individual's medical home with the assurance of privacy.[58] As a primary prevention strategy, SACHDNC advises education and the use of universal precautions such as proper hydration, accommodation of rest and recovery, and heat acclimation.

Reproductive Risk: With the majority of clinical manifestations of SCT being rare and presenting only under extreme conditions, the most significant implication of having SCT is largely considered to be its reproductive risk.[3] Specifically, those with SCT have a 25% chance with each pregnancy to have a child with SCD if their partner also carries SCT or another variant hemoglobin trait that contributes to HbS polymerization in the deoxygenated state.[47]

2.1.4 Demographics

SCD is the most common inherited blood condition in the world.[26] Its prevalence is highest in those of African, Indian, Middle Eastern, Southeast Asian, Mediterranean, Latin American, and Caribbean descent. In the United States, between 72,000 and 98,000 individuals are estimated to have SCD.[34] The majority are African American. SCD is estimated to occur in approximately one in every 400 African American, one in every 36,000 Hispanic, and one in every 80,000 Caucasian births.[30]

About 8% of African Americans are carriers of the HbS allele. The prevalence increases to 10% when other variant hemoglobin traits, such as Hemoglobin C and ß-Thalassemia, are included. The three most common forms of SCD in the United States are HbSS disease, HbSC disease, and HbS-$\beta^{0/+}$ Thalassemia.[34]

2.1.5 History in the United States

In the United States, the minority population that SCD disproportionally affects has shaped the condition's social and political narrative. The first observations of SCD in the country occurred exclusively in those of African ancestry, which fed the belief that SCD was a "race specific disease" whose "occurrence depends entirely on the presence of Negro blood."[63] Dating from the mid 19th century, the first written accounts of SCD in the United States report of characteristics suggestive of the condition in African slaves.[64] The sickle-shaped RBCs that are now iconic of the disease were first described in 1910 in the blood of an anemic dentistry student from Grenada named Walter Clement Noel. The Chicago physician, James Herrick, is credited with discovering SCD through his detailed report of this observation made in Noel's blood sample.[65] By 1923, a

number of similar findings led to the condition being named sickle cell anemia.[25] For asymptomatic individuals whose blood was observed to sickle *in vitro*, the term "sicklemia" was coined in 1926.[66] This is what is now known be the carrier state, or SCT.

Scientific advancements throughout the mid 1900s helped clarify the mechanism of SCD inheritance. In 1923, two Johns Hopkins physicians, Taliaferro and Huck, published their study of SCD that they had traced through multiple generations of a Virginia family.[67] Their paper correctly established SCD to be passed down as a single-gene Mendelian trait, yet it erroneously presented the condition as following an autosomal dominant mode of inheritance. The autosomal recessive nature of SCD was clarified in 1949 by James Neel.[47]

Experiments carried out in the mid 1900s helped to elucidate the molecular basis of SCD. In 1927, E. Vernon Hahn and Elizabeth Gillespie observed that anoxia stimulated the sickling of RBCs.[68] Electrophoresis migration studies carried out by Linus Pauling in 1949 determined that the hemoglobin molecules of affected and unaffected individuals differed in their electric charges.[69] This experiment was notable in that it was the first to directly connect a protein's chemical properties to disease pathology, and the resulting paper "Sickle Cell Anemia: A molecular disease" made SCD the first so-termed molecular disease. Sequencing of the *HBB* gene by Vernon Ingram and J.A. Hunt in 1957 traced the origin of this chemical difference in hemoglobin to the single glutamine to valine amino acid substitution.[29]

Despite this scientific progress, SCD continued to be associated with a high mortality rate throughout the early 20th century.[64] The average life expectancy for affected individuals remained under 20 years old into the 1970s.[70] With the high prevalence of infectious disease at this time, SCD-related deaths were often attributed to pneumonia or tuberculosis, with little attention given to the underlying genetic cause.[71] The high childhood mortality rate associated with SCD

disproportionately affected African American communities, thereby aggravating racial disparities in health that were gaining national attention.[64]

SCD grew as a public health and justice concern under the sociopolitical climate of the 1960s. National attention of the issue peaked in 1970, with the publication of the editorial "Health Care Priority and Sickle Cell Anemia."[72] Its author, the hematologist Robert B. Scott, argued that the amount of federal funding allocated to SCD was significantly less than other childhood genetic disorders, such as cystic fibrosis, muscular dystrophy, and phenylketonuria, relative to the population size it affected. Through reframing the shortage of funding devoted to the condition as a matter of civil rights, Scott, who himself was African American, rallied for increased public and federal backing of SCD research, screening, early diagnosis, and disease management.

Scott's paper is largely credited with stimulating the creation of SCD screening, clinical care, and education programs nationwide.[64,72,73] The year following its publication, the National Association for Sickle Cell Disease was established as the first national organization dedicated to SCD research, education, and funding.[74] Formed from the union of fifteen independent community-based SCD organizations, it persists today under the name Sickle Cell Disease Association of America. Also in 1971, President Nixon brought national attention to the issue in his Presidential Message to Congress, which highlighted deficiencies in SCD funding.[75] His speech spoke of SCD as a neglected disease and echoed Dr. Scott's concerns for an increased need for federal support for the condition. Congress responded by passing the Sickle Cell Anemia Control Act in 1972.[75,76] This legislation was the first federal program to target a specific genetic disorder.[64] Acknowledging SCD as a significant public health concern, it allocated ten million dollars for SCD screening, counseling, treatment, education, and research programs, thereby providing a ten-fold increase in funding from what had previously been available.[75] One important product of this

funding was the Hemoglobinopathy Reference Laboratory, which is based at the Centers for Disease Control and Prevention (CDC) and serves as a national reference library for state health departments, Sickle Cell Clinics, and Sickle Cell centers that test for SCD.[2] The Control Act also funded the creation of the National Sickle Cell Disease Program, as well as the establishment of 41 SCD treatment centers throughout the country.[2,49] These centers continued to expand with funding that was renewed in 2003 through the Sickle Cell Treatment Act.[77]

As funded by the Control Act, The National Heart, Lung, and Blood Institute established a Sickle Cell Branch for research into SCD natural history and therapy in 1973.[75] Under this group, the multicenter Cooperative Study for Sickle Cell Disease (CSSCD) was formed in 1977. The CSSCD was a prospective study of SCD, which aimed to better understand the condition's natural history as well as factors that influence its morbidity and mortality.[78] 3,800 participants were recruited from twenty-three institutions between 1978 and 1988. One of the most well-known studies to come out of the project was the Prophylactic Penicillin Study (PROPS) Trial, which demonstrated the effectiveness of penicillin prophylaxis in decreasing invasive pneumococcal disease in children with SCD.[5] The results of the PROPS I trial were published in the New England Journal of Medicine in 1986, prompting the National Institutes of Health (NIH) Consensus Committee, cosponsored by Health Resources and Services Administration (HRSA), to recommend universal newborn screening for hemoglobinopathies in 1987.[6] The NIH statement specified that state laws should provide voluntary universal SCD screening for all newborns, in order to allow for the timely initiation of oral penicillin to all those diagnosed.

Significant increases in the life expectancy for those with SCD have been made in the three decades following the NIH recommendation. This has largely been attributed to the introduction of penicillin prophylaxis along with pneumococcal vaccination and parental education, as enabled

through universal newborn screening for SCD.[79] In 1973, the estimated average life expectancy associated with SCD was just over 14 years.[80] Over 20% of deaths occurred prior to the age of two, with the majority due to invasive pneumococcal infection. In 1989, two years after the recommendation for universal NBS for SCD, initial results from the natural history study of the CSSCD demonstrated significant improvement in mortality rates.[70] The study, which included 2,824 participants under age 20 to represent 14,670 person-years of follow-up, found that 85% of those with HbSS disease and 95% of those with HbSC disease survived past the age of twenty years old. Additionally, the study's mortality rate of 0.5 deaths per 100 person-years (2.6%) in individuals under age 20 was found to be significantly lower than that of previous reports. Namely, the authors cited a study from 1975 where a mortality rate of 1.7 deaths per 100 person years (7.3%) was found among affected individuals under the age of 23.[81] Survival rates in SCD have continued to increase, and the majority of individuals with SCD currently live into adulthood (over 18 years old).[79]

2.2 NEWBORN SCREENING

The substantial reduction in SCD-related morbidity and mortality has largely been gained through timely intervention for affected infants that lowers their infection risk.[3] In the United States, this proceeds through newborn screening (NBS). NBS is a public health program that aims to detect within the first days of life congenital conditions for which early intervention can improve long-term health outcomes.[1,82] It has been deemed by the Centers for Disease Control and Prevention as one of the ten most successful United States' public health programs.[1] Since its

inception in the early 1960s, the NBS program has facilitated screening for over 150 million newborns.[1]

NBS primarily evaluates for genetic, metabolic, endocrine, and hematological conditions through a blood sample collected between 24 to 72 hours following birth.[83] The purview of NBS extends beyond the initial screen tests to the coordination of responding to out-of-range results, offering follow-up diagnostic testing, and providing treatment for infants diagnosed through screening.[84–86] Ongoing education of those who carry out the programs' services, as well as program evaluation are also crucial components of NBS.[87] The varied actions covered by NBS require the participation of a wide set of stakeholders, which include clinicians, the newborn's family, hospital staff, clinical laboratories, and policy makers.

A biochemical assay developed in 1961 by physician Robert Guthrie provided the initial basis for population-level newborn screening.[88,89] His method utilized a blood sample that was collected and dried onto filter paper to test for the high serum levels of phenylalanine that are characteristic of the genetic condition phenylketonuria (PKU). Studies published in 1953 had demonstrated that intervention via a low-phenylalanine diet successfully minimized the condition's severe neurological damage, thereby providing the impetus to diagnose affected infants prior to the onset of symptoms.[90] In 1963, Massachusetts became the first state to mandate universal newborn screening for PKU. By the end of that year, 29 states as well as Puerto Rico offered screening for PKU to all infants upon birth.[91]

Growing participation in NBS provided motivation to develop screening programs for other conditions whose effects may be mitigated by early treatment. Throughout the 1960s and 1970s, states began screening for other disorders that were primarily metabolic in nature. Screening panels continued to expand as advancements in technology allowed. With the

introduction of Mass Spectrometry to NBS in the 1990s, this push to grow became particularly relevant. Utilization of the technology, which allows for the rapid characterization of numerous metabolites from a single blood spot, quadrupled the number of disorders that could be affordably and efficiently detected in NBS through a single screening method.[92]

Mass Spectrometry technology remained unavailable to many states due to limited funding and access. This exacerbated disparities between programs, although they have been a defining characteristic of NBS since its inception.[93,94] Much of this variation arises from the state-run nature of NBS in the United States. Legislature is determined by state health officials, the state board of health, or a dedicated advisory committee specializing in NBS or genetics; these entities typically partner with state laboratories and/or other experts to review the available evidence prior to making recommendations.[93] As a consequence of this structure, differences are present in nearly all aspects of the programs, including screening follow-up, funding mechanisms, and whether parents can opt-out of the screening.[109]

Inconsistencies are particularly conspicuous in terms of the number of conditions included on a state's panel. In 1995, states' panels ranged from zero to eight conditions. By 1999, the difference had grown to between four and fifty conditions.[91] In this year, concern over such growing disparities prompted HRSA to appoint the American Association of Pediatricians (AAP) NBS Task Force to develop national standards for NBS panels.[95] As part of this effort to increase uniformity, the Maternal and Child Health Bureau commissioned the American Committee of Medical Geneticists (ACMG) in 2002 to devise a list of core NBS conditions to be a guide for states. In their evaluation of 81 conditions, the ACMG considered incidence and severity, as well as evidence regarding the efficacy of the currently available screening and treatment.[9] The ACMG specifically proposed three minimum criteria for a core condition: First, it must be detectable

within 24 to 48 hours of birth and prior to when it could otherwise be recognized by a physician; second, a sufficiently specific and sensitive screen for the condition must exist; and lastly, early detection and intervention must result in evidence-based benefit. This led to creation of the Recommended Uniform Screening Panel (RUSP).[96] As originally created by ACMG, the RUSP included 29 core conditions. An additional 25 conditions that may be incidentally identified during a core condition's screening yet present unclear benefits for screening and do not satisfy the screening criteria alone were named to a secondary list. While ACMG recommends that states mandate reporting of secondary conditions, it has received criticism for not providing clear, evidence-based guidelines for how to respond to a positive screening result for these conditions.[94]

The RUSP continues to grow in its number of included conditions. In 2003, the SACHDNC was formed by the United States Department of Health and Human Services (HHS) to advise the HHS Secretary in the process of evaluating candidate conditions for the RUSP, as well as other services relating to NBS.[97] In their evaluation, SACHDNC uses an evidence-based decision model similar to that initially used by ACMG that considers factors such as incidence, anticipated benefits of screening, availability of treatment and program feasibility. SACHDNC considers conditions that have been nominated by groups comprised of parents, advocacy groups, clinicians, and researchers. As of April 2019, the RUSP includes 35 core conditions and 26 secondary conditions.[96]

2.2.1 Newborn Screening for Hemoglobinopathies

Three forms of SCD, HbSS disease, HbSC disease, HbS-$\beta^{0/+}$ Thalassemia, have been included as primary conditions on the RUSP since its introduction in 2006.[9] However, population-based screening for SCD and SCT was available in individual states much earlier than this. Large-

scale screening for hemoglobinopathies was first suggested in 1970 by the development of a rapid and high-throughput screen for SCD that used dithionite to stimulate sickling of RBCs.[98] In 1972, the political and financial support brought about by the Control Act spurred implementation of screening programs across the United States. Funding from the Control Act contributed to technological advances made in 1973 that allowed for hemoglobinopathies and hemoglobinopathy traits to be screened for from the standard blood spot samples collected during NBS.[99] By 1974, ten states had mandatory screening programs, and another four states had voluntary screening programs.[2] New York became the first state to mandate universal newborn screening for HbSS disease in April 1975.[100] Over the following decade, four additional states added hemoglobinopathies to their NBS panels.[2]

SCD screening in the 1970s and early 1980s was not supported by a treatment that could be provided to those who the programs identified to have SCD. A contemporary editorial in the New England Journal of Medicine published in 1974 criticized this shortcoming, claiming that programs were "introduced before evidence that [they were] needed, desired or in the best interest of the affected community."[10] Rather, screening was argued for on the bases that it provided an opportunity to promote awareness and knowledge of sickle cell in "high-risk" populations.[10] However, these programs garnered widespread criticism for perpetuating misinformation and causing confusion and unwarranted anxiety.[11–13,101] The difference between SCT and SCD was often poorly communicated.[12] Educational materials provided to screening participants presented SCT as a milder form of SCD and did not clarify the health implications of SCT.[13] Consequently, parents restricted their children's activities and changed their diets when found to have SCT, despite no clear medical indication.[11,13] Other information provided to screening participants over-dramatized the pain and high mortality rate of SCD. The condition was described as "the killer

disease" by one promotional poster, and as "the black scourge" by a public service announcement published by the Red Cross.[10]Another brochure described the pain episodes of SCD as "caus[ing] the patient to scream and cry and assume odd postures in an attempt to get relief."[10] Through such histrionic portrayals of SCD, programs were criticized for aggravating anxiety while being unable to effectively alleviate the symptoms of those identified to have SCD.[120]

Racial controversy compounded these failings of early programs, with many explicitly targeting African Americans. In one 1974 study, the presence of a program in a state was found to be significantly associated with the proportion of its population that was African American.[102] Nine of the ten states with mandatory screening programs had total African American populations of over 200,000, resulting in more than 40% of the nation's African American population being subject to such programs. Screening policies existed for newborns, school-age children, couples applying for marriage licenses, and inmates.[10] In some states with mandatory screening laws for African Americans, children could be denied entry to school and couples denied marriage licenses if they refused screening. Many programs lacked safeguards for maintaining confidentiality. Cases of job discrimination against those identified to have SCT were common, in particular in the military.[103] Individuals also reported being denied health or life insurance after they screened positive for SCT, despite its lack of significant health effects.[103] Premarital and prenatal counseling were key features of many programs. Such counseling was accused of being coercive, rather than promoting informed choice. This led to aspersions of eugenics and dissent among targeted communities. Surveys of African Americans performed in the 1970s demonstrated a strong objection to the genetic counseling services that were offered to those with SCT."[11]

With growing controversy, many of the early programs were abandoned. However, renewed interest in SCD screening was brought about by findings of the PROPS study in 1986,

which was followed by the endorsement of the NIH for universal newborn screening for hemoglobinopathies in 1987.[6] By 1988, SCD was included in the NBS programs of 16 states, with another 14 states offering targeted screening. All but nine states had universal NBS for hemoglobinopathies by 1994.[2] In 1996, NBS for hemoglobinopathies was recommended by the American Academy of Pediatrics.[104] By 2006, all 50 states as well as the District of Columbia were offering NBS for hemoglobinopathies. New Hampshire became the last state to add the conditions to their NBS panel in this year.[2] This was prompted by inclusion of hemoglobinopathies on the RUSP, which was published earlier that year (Table 1).[9]

Table 1. Uptake of NBS for Hemoglobinopathies

State or Territory	Universal Screening Required or Available	State/Territory	Universal Screening Required/Available
Alabama	Jan 1, 1987	Montana	Jul 1, 2003
Alaska	Oct 1, 2003	Nebraska	Nov 1, 1996
Arizona	Jan 1, 1988	Nevada	July 1, 1990
Arkansas	Oct 1, 1988	New Hampshire	May 1, 2006
California	Feb 7, 1990	New Jersey	Apr 1, 1990
Colorado	Jan 1, 1979	New Mexico	Oct 10, 1995
Connecticut	Jan 1, 1990	New York	Apr 1, 1975
Delaware	July 1, 1985	North Carolina	May 2, 1994
District of Columbia	Jan 1, 1986	North Dakota	Apr 1, 2003
Florida	Jan 1, 1989	Ohio	Jul 1, 1989
Georgia	Oct 1, 1998	Oklahoma	May 1, 1991
Hawaii	Jul 1, 1997	Oregon	Feb 1, 1995
Idaho	May 19, 2004	Pennsylvania	Sep 28, 1992
Illinois	Feb 1, 1989	Rhode Island	May 1, 1990
Indiana	Jul 1, 1985	South Carolina	Jul 1, 1987
Iowa	Feb 5, 1988	South Dakota	Jun 1, 2005
Kansas	Jul 1, 1993	Tennessee	Jan 1, 1988
Kentucky	Jan 1, 1995	Texas	Nov 1, 1983
Louisiana	Jan 1, 1992	Utah	Sep 24, 2001
Maine	Jul 1, 2001	Vermont	Feb 4, 1996

Table 1 Continued

Maryland	Jul 1, 1985	Virginia	Jul 1, 1989
Massachusetts	Mar 26, 1990	Washington	Nov 1, 1991
Michigan	Jul 1, 1987	West Virginia	Jul 1, 2003
Minnesota	Jan 1, 1988	Wisconsin	Oct 31, 1988
Mississippi	Jan 1, 1990	Wyoming	Jan 1, 1987
Missouri	Apr 1, 1989		

From Kavanagh et al. (2008) [21]

In Pennsylvania, HbSS disease was introduced to the NBS panel in April 1992. Under the Newborn Child Testing Act (35 P.S. § 621, et. seq.), all newborns are required to receive screening unless their parent or legal guardian refuses on the basis of religious objection.[105] There is no fee for NBS in Pennsylvania.[105] The program occurs under the oversight of the Pennsylvania Department of Health, which contracts with commercial laboratories to perform the testing.[23] Follow-up in response for a positive screen for a hemoglobinopathy or hemoglobinopathy trait is determined by the Division of Newborn Screening and Genetics Bureau of Family Health under the Pennsylvania Department of Health.[23] Screening results must be reported to the Department of Health's Newborn Screening and Follow-up Program, the infant's primary care provider (PCP) listed on the filter paper, and the birthing facility. In the case of an abnormal result, the PCP is most commonly responsible for notifying the infant's parents and ensuring completion of the necessary follow-up, referral, and/or diagnostic procedures. However, hemoglobinopathies are an exception, with follow-up tasked to the SCD centers. Currently, hemoglobinopathies account for the highest proportion of disorders identified by the states' NBS program.[106] The most commonly identified form of SCD in both Pennsylvania, as well as in the United States, is HbSS disease, followed by HbSC disease, HbS-β^0 Thalassemia, and HbS-β^+ Thalassemia.[23]

Through the current NBS technology, SCT is identified incidentally through screening for SCD. However, SCT does not require immediate care for the infant, and no consensus currently exists regarding appropriate follow-up in response to the positive NBS result.[21,73,107] While

identification of SCT does not clearly align with the public health program's stated intent, the decision of many states' NBS programs to share this information with families was largely shaped by a statement put forth by the Institution of Medicine (IOM) in 1994.[1,8] In its report entitled "Assessing Genetic risk," the IOM argued that although SCT status was not purposefully sought out during screening, the state was obligated to share this genetic information, as it belonged to the infant and his or her family.[21]

To guide physicians in responding to a positive screen for SCT, the ACMG published an ACTion (ACT) sheet for SCT in 2012.[108] The ACMG makes ACT sheets for all NBS conditions to serve as instructions for physicians in their follow-up for a positive screen. Specific actions depend on the condition but typically include prompt notification of the family, further diagnostic evaluation, and treatment for affected newborns. For an abnormal hemoglobin trait, providers are directed to perform confirmatory testing, report the screening results to the state, and offer family members referral for personal hemoglobinopathy screening and genetic counseling. The SCT ACT sheet also advises physicians to inform families of the good prognosis for SCT and to reassure them that infants with SCT do not have the clinical symptoms of SCD. The clinical considerations for SCT specified by the ACT sheet include the reproductive risks for carriers, as well as risks for renal complications, namely hematuria in older children and adults, and potentially other complications in the case of extreme exertion, dehydration, and hypoxia.

There remains significant variation among programs in how the information regarding a positive SCT screen through NBS is disseminated to families.[21] A PCP or specialty provider often receives the initial notification from the laboratory, and in few states is contact with the family aggressively pursued. In a report from the National Newborn Screening and Genetics Resource Center in 2009, about 15% of infants with a positive screen for SCT were found to receive follow-

up diagnostic testing; however, this follow-up testing is not universally recommended by all SCD centers.[109] Another study performed in 2007, which was one year following inclusion of SCD in the RUSP, surveyed NBS program coordinators regarding their follow-up protocols in response to a positive screen for SCD or SCT.[21] The questionnaire asked which stakeholders were directly notified following a positive screening result, by what means they were informed, and how it was ensured that this notification was received. Over one-third of programs did not report having any protocol for follow-up for a positive SCT screen. Among those programs that did, significantly fewer stakeholders were directly notified following a positive NBS for SCT as compared to SCD (2.4 versus 3.4, $p < 0.0001$). Only 37% of programs reported a process for directly notifying families regarding SCT results. Finally, while all programs reported directly notified the infant's pediatrician regarding a positive NBS for SCD, 88% of programs notified pediatricians in the case of SCT. Based on these findings, the study's authors called for resources and guidelines to be developed for provider regarding communication about SCT screening through NBS.[21]

2.2.2 Screening Guidelines

The substantial variation in NBS programs' policies regarding SCT results compounds uncertainty about the program's true appropriateness. As it exists in public health generally, an ethical challenge exists for the program to balance public benefit with individual liberties.[110] A number of criteria and systems have been developed to guide these considerations in the implementation of public health screening programs. They may be applied to an evaluation of the appropriateness of disclosing positive SCT status identified through NBS.

As commissioned by the World Health Organization (WHO) in the mid 1960s, the Wilson-Jungner criteria remain one key set of guiding principles (Table 2).[111] The ten criteria describe

characteristics of a condition and its method for testing, diagnosis, and treatment needed to justify screening. The criteria also consider cost, availability of resources, and public reception to the screening program.

Table 2. Original Wilson-Jungner Criteria

1	The condition sought should be an important health problem.
2	There should be an accepted treatment for patients with recognized disease.
3	Facilities for diagnosis and treatment should be available.
4	There should be a recognizable latent or early symptomatic stage.
5	There should be a suitable test or examination.
6	The test should be acceptable to the population.
7	The natural history of the condition, including development from latent to declared disease, should be adequately understood.
8	There should be an agreed policy on whom to treat as patients.
9	The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.
10	Case-finding should be a continuing process and not a "once and for all" project.

The Wilson-Jungner Criteria remain widely regarded as the "gold standard" for public health screening.[112] United States policy makers are generally guided by the criteria in their evaluation of potential additions to their states' NBS panel; however, political pressure, availability of technology, and financial considerations may also factor into their decisions.[113] A 2006 review of international NBS practices criticized the wide variability in how the Wilson-Jungner criteria were being interpreted and applied throughout the United States.[114] The authors largely attributed this lack of consistency to rapidly advancing technological capabilities for

screening that were outpacing policy-maker's ability to evaluate the programs' appropriateness. An updated set of Wilson-Jungner criteria was published in 2008 in recognition of this challenge (Table 3).[112] The revised criteria seek to have greater applicability to genetic medicine and place greater emphasis on the contemporary medical values of equity, access, and scientific evidence. They also acknowledge that certain legal, ethical, logistical, and social factors may obviate a particular screening program.

Table 3. Modified Wilson-Jungner Criteria

1	The screening program should respond to a recognized need.
2	The objectives of screening should be defined at the outset.
3	There should be a defined target population.
4	There should be scientific evidence of screening program effectiveness.
5	The program should integrate education, testing, clinical services and program management.
6	There should be quality assurance, with mechanisms to minimize potential risks of screening.
7	The program should ensure informed choice, confidentiality and respect for autonomy.
8	The program should promote equity and access to screening for the entire target population.
9	Program evaluation should be planned from the outset.
10	The overall benefits of screening should outweigh the harm.

In 2011, four past and present members of the U.S. Preventive Services Task Force (USPSTF) proposed an alternative strategy for evaluating screening programs.[115] The USPSTF is a panel of national experts, which makes evidence-based recommendations regarding screening and other clinical preventative services.[116] The publication by Harris et al. reviewed the experience

of the USPSTF in evaluating screening programs in the United States from 1997 to 2011 to put forth criteria that addressed stated shortcomings of the Wilson-Jungner criteria. Their system, which aimed to better capture the methods found useful by the USPSTF for program evaluation, contrasted the Wilson-Jungner criteria's "checklist" system in favor of a "Balance Approach." Using this latter system., a screen's anticipated benefits are weighed against its anticipated harms with regard to current scientific evidence and available resources in order to determine its appropriateness (Table 4).[115] The authors also emphasize that the particular cultural needs of the communities being screened should be considered.

Table 4. Summary of Considerations for Estimating a Screening Program's Benefits and Harms

Magnitude of Potential Benefits		**Magnitude of Potential Benefits**	
1	Probability of an adverse outcome without screening	**1**	Frequency of false-positive screening tests
2	Degree to which screening identifies all people who suffer the adverse outcome	**2**	Experience of people with false-positive results
3	Magnitude of incremental health benefit of earlier versus later treatment resulting from screening	**3**	Frequency of over diagnosis
		4	Experience of people who are over diagnosed
		5	Frequency and severity of harms of workup and treatment

2.2.3 Potential Benefits of Sickle Cell Trait Notification

In an evaluation of the program's appropriateness, a primary argument for sharing SCT NBS results concerns reproductive choice.[8,117] Namely, programs that notify parents of the

incidental NBS finding seek to inform the prenatal decisions of the infant and their family members who may have an increased chance of having a pregnancy affected with SCD. Professional guidelines recognize that informed reproductive decisions regarding SCD are aided by an awareness of one's personal trait status along with an understanding of the condition's inheritance pattern.[19,20] Studies that have been carried out in the United States to assess this knowledge have primarily focused on African American and other minority communities, as these are where SCD is the most prevalent.[30] These assessments have largely determined that the current level of relevant knowledge is likely insufficient for informed decision-making. Importantly, these studies have also found that the affected communities view this lack of SCT awareness to be a significant concern.

Sickle Cell Knowledge: Medical guidelines recommend screening and counseling to clarify personal SCT status and provide education about SCD inheritance. Current American College of Obstetricians and Gynecologists (ACOG) guidelines recommend hemoglobinopathy screening through a complete blood count with RBC indices for all women who are either pregnant or considering pregnancy; for those whose RBC indices indicate a low mean corpuscular hemoglobin or mean corpuscular volume indicative of a hemoglobinopathy, as well as women of high-risk ancestries, hemoglobin electrophoresis should also be performed.[20] Hemoglobinopathy screening is also central to the reproductive counseling outlined in current consensus guidelines for SCD. Developed by the National Heart, Lung, and Blood Institute (NHLB) of the National Institutes of Health (NIH), the guidelines specify that hemoglobinopathy screening should be offered to clarify the SCT status of the other individual in a couple where one is known to have SCT or SCD.[19] Additionally, at-risk couples should be offered genetic counseling to discuss the potential for an affected pregnancy. Couples are recommended to make a "reproductive life plan"

that relates to their desires either to have or to not have children. Both contraceptive and preconception counseling, including pre-implantation genetic diagnosis and prenatal diagnostic testing following spontaneous conception, are included in the guidelines, which emphasize individual choice.

A number of survey and interview-based studies have sought to assess knowledge levels regarding SCD inheritance and personal SCT status, primarily among high-risk demographics (Table 5). These studies have recruited participant through a variety of means and locations and have utilized different questionnaires and survey methods. However, they have generally found that while participants are aware of the congenital nature of SCD, they have a poorer understanding of its particular inheritance pattern. Additionally, there is a consistent lack of awareness regarding personal trait status, in spite of professional guidelines and programs that promote screening.

In 1994, Wright et al. interviewed 147 African American between the ages of 18 and 50 who visited the emergency room of a large urban medical hospital for minor injuries.[118] Nearly all individuals (98%, 144/147) had heard of SCD, and about three-quarters (73%, 107/147) were aware of its genetic basis. However, knowledge of personal trait status was not as high, with only thirty-one percent (46/147) knowing whether or not they had SCT. Women were more likely to know their trait status than men, as were patients with a family history of SCD or SCT compared to those with no known family history.

A telephone survey of African American women of reproductive age (between 18 and 30 years old) was carried out in 2005 in St. Louis, Missouri, where universal NBS for SCD has been available since 1989.[119] Boyd et al. used random-digit dialing to recruit participants, yet one-third of the 241 women contacted had to be excluded from the survey, as they had not heard of SCD. Next, an assessment of SCD knowledge was administered over the telephone to those who were

aware of SCD. While 91% of the women understood that individuals were born with and could not later develop SCD, less than 10% were able to correctly describe its inheritance pattern. The remaining 90% of women answered that SCD "skipped generations" and could occur in a pregnancy where one parent had neither SCT nor SCD. Knowledge of personal trait status was relatively high compared to other studies, yet this finding was calculated after excluding the nearly one-third of women contacted for the study who had not heard of SCD. Ninety percent of participants confirmed that they knew whether they did (14%) or did not (76%) have Sickle S trait. However, awareness of carrier status was not as great for other variant hemoglobin traits. Twenty-seven percent of women stated that they knew whether or not they were a carrier of HbC trait, and 10% of women knew their ß-thalassemia trait status.

In 2006, Treadwell et al. interviewed 316 men and women of reproductive age (ages 18 to 44 years old) in an ethnically diverse, urban community of northern California.[120] California has required universal SCD screening through NBS since 1990.[2] Unlike the majority of studies of either exclusively or majority African American participants, only 36.4% (115/316) of participants surveyed by Treadwell et al. identified as African American. When asked if both parents must have SCT to have a child with SCD, nearly nine out of ten surveyed individuals (86.2%, 261/316) answered correctly. However, a relatively small proportion, 15.9% (45/316), reported knowing whether or not they had SCT. Lower knowledge of personal SCT status in spite of higher general knowledge may be related to the more racially diverse population of the study. As the current ACOG guidelines recommend hemoglobinopathy screening only to those of certain ancestries, a smaller proportion of this study's participants may have been covered by the screening guidelines as compared to other studies.

In 2007, Gustafson et al. administered an anonymous questionnaire on health beliefs and knowledge relating to SCD to 101 African American women over 18 years of age at an Obstetrics and Gynecology clinic of a large women's hospital in Pittsburgh, Pennsylvania.[121] Over three-quarters (79.2%, 80/101) of women knew that SCD was genetically inherited, yet only half (49.5%, 50/101) recognized that a gene mutation had to come from *both* parents for their child to have SCD.

In a 2009 study, Acharya et al. recruited 53 African American individuals who either had SCT themselves or had a child with SCD or SCT from a sickle cell clinic and sickle cell non-profit organization in Chicago, Illinois.[122] Hemoglobinopathies have been included in the Illinois NBS program since 1989.[2] At the time of the study, parental SCT notification proceeded through a letter sent either from the birth hospital or from the Sickle Cell Disease Association of America under state contract with the Illinois Department of Health.[122] Participants answered an anonymous, validated questionnaire on SCD genetics and screening. Despite all participants having personal experience with SCT or SCD, their responses showed significant misunderstanding of the condition's inheritance. Nearly all knew that SCD was a genetic condition (89%, 47/53) and not transmitted via physical contact (89%, 47/53). However, less than half (40%, 21/53) were aware that both parents needed to have SCT or SCD for their child to be affected with SCD. Sixty-eight percent (36/53) of respondents answered all ten knowledge questions correctly. Mean knowledge score was significantly lower for those parents who did not have a child with SCD, as compared to those who did (78% versus 58%, $p = 0.002$).

Finally, a study carried out by Lang et al. in 2009 interviewed 387 post-partum women in Chicago hospitals in order to determine their attitudes and understanding of NBS screening for SCD.[18] At the time, the Illinois NBS program notified parents of their infant's positive SCT

screening result through a letter that was mailed shortly after their infant's birth.[18] Approximately 73% (282/387) of participants were African American, and 8.8% (34/387) reported having SCT. One individual had SCD. Ninety-six percent of women in the study had heard of SCD. A trained interviewer asked these individuals a set of knowledge questions regarding SCD. Sixty percent (232/387) of respondents believed SCT could develop into SCD, and 71% (275/387) believed that an individual with SCD could have a child with SCD even if their partner was not a carrier of a variant hemoglobin trait. The mean knowledge assessment score of 66% was deemed by Lang et al. to indicate a "significant knowledge gap" regarding the health and reproductive implications of SCT in this population.[18]

A lack of SCD knowledge persists in many of those communities at greatest risk for SCD. A number of studies, which have examined trait status awareness in relation to access to prenatal and general medical care, show that such care for high-risk communities is deficient and when present, may still insufficiently ensure that individuals are aware of their SCT status. In a 2010 study by Lang et al., 100 Chicago-area mothers notified of a positive NBS result for SCT through a mailing within the past year were surveyed over the phone or in person (93% and 7%, respectively).[17] Participants were 95% (95/100) African American, with a mean age of 26 years old. Sixty-two percent reported not having a personal doctor other than an obstetrician, and 83% reported having no insurance. Less than half (40%) reported knowing their SCT status prior to this pregnancy, even though it was not their first pregnancy for over two-thirds (69%) of participants. However, Lang et al. did not report whether a greater awareness of personal SCT status was more likely to be found in those who had previously been pregnant.

A similar lack of awareness of SCT was found among African American men and women recruited from a community-based health organization in Pittsburgh, Pennsylvania, in spite of

greater reported access to prenatal and medical care.[16] Forty-two percent (14/33) of participants were not aware of their personal SCT status, and the majority (74%) did not know the SCT status of their partner. This relatively low awareness of personal SCT status was found even though 97% of participants had health insurance and 83% did not report having difficulty accessing medical care due to its cost, indicating the presence of other barriers to SCT awareness besides access to healthcare among at-risk communities.

Table 5. Summary of Sickle Cell Knowledge Studies

Study	Population	Survey Method	Percent Correct		
			Genetic Condition Question[1]	Autosomal Recessive Question[2]	Personal Trait Status
Wright et al. (1994)[118]	147 African American men and women aged 18 to 50, admitted to the emergency department of a large urban university hospital	In-person Interview	73%	-	31%
Acharya et al. (2009)[122]	53 parents of a child with SCD or SCT, or who had SCT themselves, recruited from University of Chicago SC clinic and SC community-based organization	In-Person Interview	89%	77%	94%
Lang et al. (2010)[17]	100 mothers of newborns with SCT identified via Illinois NBS; 98% African American, mean age 26 years old	Telephone Interview	-	67%	45% before pregnancy

Table 5 Continued

Boyd et al. (2005)[119]	162 African American women, aged 18-30, in the St. Louis, Missouri area contacted via random-digit dialing	Telephone Interview	91%	"less than 10%"	90%
Treadwell et al. (2011)[120]	316 men (34%) and women (66%), 36.4% African American, aged 18-44, recruited from the neighborhood surrounding northern California Comprehensive SC Center	In-person Interview	91.1%	86.2%	15.9% (n = 45)
Gustafson et al. (2007)[121]	101 African American women over age 18 seen at Obstetrics and Gynecology clinic in Pittsburgh, PA	Anonymous Survey	79.2%	49.5%	-
Kladny et al. (2005)[24]	43 mothers of newborns identified to have SCT via Pennsylvania NBS who received an educational video about SC	Telephone Interview	93%	90.7%	-

[1] *Question assessed participant's understanding that SCD was a health condition an individual is born with, and is not contagious*

[2] *Question assessed participant's understanding that a genetic contribution had to come from both parents for a child to have SCD*

Transmission of Sickle Cell Knowledge: Generally low knowledge levels regarding sickle cell that persist in spite of medical guidelines intended to promote awareness. This suggests that more effective strategies are needed to ensure transmission and retention of this health information. Personal connections have been found to be central to the promotion of health

knowledge in African American communities, where family, friend, and community resources are looked to as primary resources.[16,122–124] While Treadwell et al. found that only 16% of participants knew their SCT status, for over half of those who did (53%), this knowledge had been gained through discussions with family members.[120] When Acharya et al. asked participants about their personal SCT status and general SCD knowledge, those who did not have a child with SCD most often designated family members to be their source of information, as well.[122] The study also found relatively high awareness of personal trait status (94%), but substantial confusion about SCD inheritance: 60% incorrectly responded to the question regarding autosomal recessive inheritance. In the focus groups held by Long et al., "reliance on personal experience" was identified as a prevalent theme in participants' discussion of their perceptions and knowledge of SCD.[16] However, similar to those findings of Acharya et al., this theme was found to be associated with greater confusion and misconceptions about SCD inheritance. It was postulated that this was due to participants trying to make sense of patterns of SCD inheritance observed in their own family.[122] In sum, these findings indicate that social networks may be especially effective at promoting awareness of personal SCT status but less so at disseminating more general information regarding the condition and its inheritance.

Surveys of disclosure patterns of parents notified of their infant's positive SCT status through NBS indicate that the program promotes sharing of the health information within familial networks. The great majority of parents report that they intend to discuss their child's positive trait status and its implications with their son or daughter at an older age. In one telephone survey of 300 families who were seen at a pediatric Sickle Cell clinic in Pittsburgh, Pennsylvania for genetic counseling following identification through NBS of an abnormal hemoglobin trait, 91% (104/114) responded that they planned to inform their child about the NBS result following counseling for

the screening results.[22] Additionally, when Lang et al. surveyed mothers notified about their infant's positive SCT result through a letter sent through the Illinois NBS program, 99% (99/100) expressed that trait status should be shared with the infant.[17] Thirty-eight percent of respondents indicated they planned on informing their infant when he or she was a teenager or young adult. The remainder specified a younger age, with a mean specified age of sharing to be 8.6 years.

Studies indicate that families are inclined to share this information with other close family members as well. In the study by Lang et al., mothers of infants found to have SCT through NBS were asked which individuals they felt should know this health information about their child. Ninety-seven percent expressed that they intended to speak about this information with their partner.[17] Greater than 90% of mothers also stated that they felt first-degree relatives should also have this information: 92% planned to share this information with their siblings, 97% with their parents, and 93% with their infant's siblings. There was less consensus that "other relatives" should know about their infant's SCT status, with 63% of participants reporting that they would share this information with more distant family members. Among those who said that they would *not* share this information with the specified individual, the majority (31%, 31/100) responded that this was because this information was not relevant to them, rather than that they did not want them to know that their baby had SCT (6%, 6/100). In the greater context of the study, Lang et al. interpreted these disclosure patterns to demonstrate that the notified mothers possessed a good understanding of who should also know the trait letter's information. Lang et al. called for further research in order to determine whether mothers did actually share this information, and if so, when and how this information was imparted.

As Lang et al. indicates, reported intentions to share SCT status may not accurately represent true disclosure patterns. This highlights a primary shortcoming of the NBS program,

which is that the health information it provides comes prematurely for the infant. Those who receive SCT screening through NBS must be told their positive trait status at an older age for the program to have this benefit. For those who are relayed the information, they may not remember their carrier status or appreciate its implications by the time they are of reproductive age. This timing has been criticized by professional organization, including the ACMG, the American Society of Human Geneticists (ASHG), and the AAP.[125–127] Statements from these groups present carrier screening in infants and children as threatening their autonomy to choose whether or not to pursue carrier screening for SCT while presenting them with no true health benefit.

Ideally, carrier screening is offered prenatally, when the information is most relevant to the individual.[19] While it is not the case for the infant, trait notification through NBS often comes at an opportune time to inform the reproductive decisions of the infants' parents, for at least one parent must also have SCT. If the other partner also has SCT of SCD, the couple has a chance for a future pregnancy of theirs to be affected with a clinically significant hemoglobinopathy.

NBS may serve to inform parents of their own positive SCT status at equivalent rates to prenatal screening. When Acharya et al. asked mothers how and when they learned of their SCT status, approximately equal proportions named prenatal screening and NBS: 36% (19/100) of women reported they had learned prenatally, while 26% (14/100) reported they had learned after their child's NBS and 11% (6/100) from their own NBS.[122]

Evidence supports that NBS results may provide information for the parents at a higher rate than they do for the child. The reproductive benefit of parents and other close relatives has been posited as a main justification for NBS trait notification, yet a question exists whether this is consistent with the current aims of NBS. This goal of informing parents' reproductive choice extends beyond the program's traditional scope, which is to provide interventions to affected

infants in a timely manner to significantly improve their health outcomes.[1,111] However, reproductive benefit has been gaining increasing support as a reason for NBS programs.[117,126] In one 2007 survey of healthcare providers, 78% agreed that one purpose of NBS is to provide an infant's carrier status to their parents. The majority of providers (68%) also agreed that NBS should inform parents about their own reproductive risk.[128] In another study examining ethical issues in pediatric genomics, 90% of American PCPs surveyed agreed with the statement, "an important goal of newborn screening is to identify and counsel parental carriers before the next pregnancy."[129]

Whether the NBS results are more salient for the infant or for his or her family members may be made less of concern when greater SCD awareness in general has been identified as a priority by African American communities. This is an important consideration in light of criticism that early screening programs were undesired by those they targeted.[49,103] A consideration of the NBS program's appropriateness must heavily weigh the views of the communities it most affects. This is highlighted by contemporary ethical guidelines that emphasize community reception and cultural sensitivity in determining the appropriateness of a screening program.[112,115] Under this criterion, NBS for SCT is supported by findings that increased awareness of SCD is desired by African American communities.[14–16,120] Furthermore, this knowledge appears to contribute to more accurate risk perception and greater reception of screening in these communities.[16,130]

Community-based studies have provided the support for the receptiveness of at-risk communities to SCD educational programs. In 2016, Housten et al. offered hemoglobinopathy education and screening in St. Louis, Missouri to African American men and women between 14 and 60 years old who were recruited from Qualified Health Centers, as well as community health events at churches and public libraries.[15] The program was driven by requests from an advocacy

group comprised of members of an African American Fraternity as well as a SCD treatment and education team, both of which were based at the local university. When members of these organizations were polled, 100% agreed that SCD knowledge and personal SCT status should be made a priority for adolescents and adults in St. Louis who are at the greatest risk for having a pregnancy affected with SCD. Both organizations expressed that SCD education was needed to empower individuals to make informed decisions about their reproductive health. Similarly, in an open-ended survey of 300 African American men and women aged 18 through 35 years old who did not know their SCT status, Mayo-Gamble et al. asked participants their beliefs and perceptions about SCT and SCT screening.[131] Perceived lack of knowledge about SCT and perceived health benefits of SCT screening were both identified as major themes through qualitative thematic analysis of the discussion transcripts.

Similar concerns have been identified in more targeted studies of those who are aware of their SCT status. When focus groups of African American adults who either had SCT or SCD were asked about their beliefs regarding reproductive choice in relation to sickle cell, a major concern of participants was the lack of understanding about SCD inheritance and personal trait status and how this affected reproductive choice.[132] The groups specified three pieces of information to be clarified for people of reproductive age in their community: 1) the genetic transmission of SCD, 2) the distinction between SCD and SCT, and 3) that SCD could not be transmitted like a cold or a sexually transmitted infection. Participants agreed that SCT status should be established before pregnancy in order to inform couples about their chance of having an affected pregnancy. Additionally, they noted that a key barrier to screening was an insufficient understanding about how an infant could be born affected with SCD, as well as an under-appreciation for the relevance of knowing one's personal SCT status.[132]

The value of screening and genetic testing for hemoglobinopathies and hemoglobinopathy carrier status was specifically addressed in focus groups held by Long et al.[16] The 35 participants, who were majority female (91%, 32/35) with a mean age of 53, were recruited from a community-based health program focusing on racially segregated neighborhoods affected by poverty and chronic disease in Pittsburgh, Pennsylvania. Moderator-led discussions sought to more fully clarify the attitudes and perspectives of African American individuals on SCD and barriers to awareness. Through qualitative thematic analysis, a value of awareness brought about by genetic testing was identified as a major theme. Knowledge about a genetic condition was recognized as allowing for understanding of recurrence risks and permitting one to modify related behaviors.

With a similar aim as that of Long et al., Asgharian et al. interviewed 34 African and African Caribbean women with SCT to gain insight into how knowing one's carrier status influenced reproductive decisions.[130] The authors also identified a theme of understanding the genetic transmission of SCD to be important for making informed choices regarding pregnancy.

Finally, in their study about SCD health beliefs and knowledge of reproductive-age African American women, Gustafson et al. found a high perceived benefit to hemoglobinopathy screening and counseling among participants.[121] Participants were asked to rate on a five-point Likert scale their perceived usefulness of knowing their SCT status and knowing their partner's status for planning for pregnancy. Scores of 4.32 and 4.43 respectively indicated that the participants viewed this information to be valuable for reproductive decisions. A higher average SCD knowledge score was significantly associated with a greater perceived benefit of screening, yet not with a higher perceived risk of having a child affected with SCD. However, A higher perceived risk of having an affected child did significantly correlate with a greater understanding of recessive inheritance

and SCD inheritance patterns. In this finding, Gustafson et al. emphasized the importance of promoting understanding of the mode of SCD inheritance in counseling and education.

2.2.4 Potential Risks of Sickle Cell Trait Notification

As they exist in any screening program, a number of risks may be realized by SCT notification through NBS. These include the potential for psychological, social, and/or emotional harm from impaired self-image, stigmatization, discrimination, and undue parental anxiety. Many of these risks pertain to screening for SCT, as well as for SCD and for genetic screening programs more generally. The relative weight of these harms as compared to the benefits must be considered when SCT does not pose an immediate health concern for the infant.

Providing genetic information can alter how an individual is seen by others and also how they see themselves. This may result in stigmatization, where the perception of an individual as undesirable leads to their devaluation as well as possible discrimination and altered behavior toward them.[133–135] A genetic diagnosis may cause one to feel shame, distress, secrecy, isolation, and damage to self-perception.[134] In the medical context, both stigmatization and emotional harm can lead to the additional harm of causing a person to mistrust or under-utilize healthcare services.[134] Both the infants and their family members are vulnerable to such harms in NBS programs which notify families of positive SCT results.

Historical precedent exists for this concern. One major criticisms of the initial sickle cell screening programs was that they led to stigmatization of sickle cell carriers.[10,11,49] Studies that have aimed to assess the burden of stigma associated with SCT have generally found that stigma associated with SCT may be anticipated more than actually felt by individuals with SCT. Additionally, those with SCT have not been found to view themselves or their health more

negatively on account of their carrier status. Consistent with this first point, a fear of stigma directed toward SCD and medical conditions in general has been identified as a barrier to hemoglobinopathy screening and related follow-up services among at-risk communities.

Dating from the early 1980s, one of the earliest studies on the topic found minimal evidence that the self-perception of sickle cell carriers was harmed by their awareness of having SCT. In this study, African American individuals with SCT were asked to respond to a Health Orientation Scale (HOS).[136] The HOS survey consisted of 12 pairs of opposing adjectives (Good – Bad; Sad – Happy; Sick – Health; etc.), which participants were asked to assign to how having SCT made themselves or others feel. Responses were rated on a five-point Likert scale. The HOS survey was also administered to study participants who were also African American but did not have SCT. This latter group was more likely to report a negative attitude toward individuals with SCT than those who did have SCT.

In 2009, Acharya et al. administered the same HOS-based survey to 53 African American or non-Hispanic adults with SCT from the Chicago area.[122] Participants answered the survey as it related both to their perception of themselves, as well as how others perceived them. The average score on the HOS scale was 3.8, indicating an overall positive self-image possessed by those with SCT. This average score was higher than that found previously in the earlier study, which had also concluded that sickle cell carriers do not view their health negatively impacted by having SCT.[136] Acharya et al. interpreted these findings to indicate that sickle cell carriers' self-image had improved since the initial days of screening programs, while admitting that the unavailability of raw data from the earlier study precluded statistical testing to determine if this increase was statistically significant. Similar to the earlier study's findings, Acharya et al. also found that participants who did not have SCT themselves reported viewing SCT more negatively than those

who knew that they were carriers ($p < 0.05$). This was the case for overall score (3.8 versus 3.2, $p < 0.05$), as well as with ten of the 12 individual questions ($p < 0.05$).

Acharya et al. additionally measured stigma with a questionnaire originally developed in the late 1990s for a similar purpose for HIV.[137] Participants were asked to rate eight statements on a one to five scale, with five representing the highest stigma. The mean score was 1.6, indicating low stigma. For all but one of the eight statements, less than five percent of responses indicated any degree of perceived stigma. All study participants disagreed with the statement "I worry about people discriminating against me" on account of having SCT. Acharya et al. concluded that those with SCT did not feel stigmatized on account of their carrier status. The authors did note the limited generalizability of their data, given that stigma may differ based on sex and socioeconomic class. This is an important limitation of all studies that survey one population in order to more generally characterize a community's perceptions, attitude, and beliefs toward sickle cell screening.

Evidence supports that among African American communities, there is a perception that those with SCT are viewed as undesirable or unhealthy.[16,120] Even in the context of positive self-image, this fear may engender secrecy about one's positive trait status and serve as a deterrent for hemoglobinopathy screening in those of un-clarified trait status. Effective SCT screening requires notified families to feel comfortable seeking follow-up testing, education, and counseling from their providers. It also calls for notified individuals to share the health information with close biological relatives who may also be at greater risk for having a pregnancy affected with SCD. Fear of stigmatization that inhibits such helpful sharing not only diminishes the utility of the health information, but also may impede the newborn's care and harm familial dynamics.

A desire for secrecy due to perceived stigma has been identified as a barrier to effective SCT follow-up with medical providers among African American communities. In their focus

groups, Treadwell et al. elicited the perceptions of participants on how screening and other medical services for hemoglobinopathies could be improved.[120] A theme of stigma was identified as a barrier to following up on a positive screening result for SCT in two of the three focus groups: 1) that of individuals who had a first-degree relative with SCD or SCT or who themselves had SCT or SCD, and 2) that of African American men and women from the surrounding community. Terms such as embarrassment, taboo, stigmatization, fear, and ostracism were prevalent in both groups when discussing SCT. One participant remarked, "children…face stigmatization, fear and ostracism" and another that "people…with sickle cell are embarrassed; being unhealthy is taboo." Stigmatization was not identified in the discussion of the third focus group, which consisted of healthcare providers who regularly worked with individuals affected with SCD. From this, Treadwell et al. posited that providers may not appreciate how related anxiety may be impeding families to pursue follow-up in response to a positive screen for SCT. Trait notification could thereby hinder the establishment of an effective alliance between families and their child's provider in a crucial time of the infant's care. Gaps in communication between the African American population and healthcare providers have been well-characterized and a contribute to race-based health disparities in the United States.[101,138,139] Trait notification could exacerbate such differences.

The disclosure of a newborn's SCT status may also jeopardize familial relationships. Parents may experience guilt or shame in response to their child's positive SCT screen or blaming the other parent if they believe them to have passed on SCT to the child.[11,135] Trait notification may also expose non-paternity or contribute to distress over a potential future pregnancy being affected with SCD.[11,82] The potential for these harms were demonstrated in one study, in which interviews of 34 African and African Caribbean women with SCT were conducted to gain insight

into how their carrier status influenced reproductive decisions. Participants expressed that a fear of rejection inhibited them from discussing SCT status with their partners.[130]

The theme of shame and stigma associated with disease in a family was similarly identified as a barrier to effective sharing of knowledge in the focus groups held by Long et al.[16] The study utilized qualitative thematic analysis to elucidate the attitudes and perspectives of African American individuals on SCD and barriers to education and awareness. A feeling of shame about personal and family health history, which discouraged open communication within families, was identified as an impediment to greater knowledge of SCD. However, one participant remarked that she thought, "more families are talking about it. It's not seen as you have to be ashamed of it," indicating that this concern may be diminishing in younger generations. This temporal shift is supported by previously presented findings, which indicate that most parents notified of their infants' SCT status via NBS intend to share this information with close relatives.

Parents may experience guilt over their child being born with SCT yet there is little support that they blame their partners. In the study of Kladny et al. carried out in the Pediatric Sickle Cell Clinic of Children's Hospital of Pittsburgh (CHP), 114 families who received genetic counseling following a positive hemoglobinopathy trait screen via NBS were anonymously surveyed about their feelings regarding the screening.[22] Nineteen percent of families reported a feeling of guilt or of being upset over their child having SCT. However, only 4% reported that they believed their partner blamed them for their child's trait status. Participants were not asked whether they blamed their partner for their child's SCT status. Additionally, blame was not identified when Gallo et al. held focus groups to elicit the beliefs and emotions of individuals with SCD or SCT regarding informed reproductive decision-making.[132] Participants either had SCD themselves, or they were a parent of a child with SCD and at least 36 years of age. This age group was selected, as they

were more likely to have already made reproductive decisions. While many individuals expressed a sense of blame associated with a child's inheritance of SCD, this was not the case for SCT.

Another primary risk of screening for parents is the anxiety that can arise in response to receiving a genetic diagnosis for one's child. Previous studies that have looked at the disclosure of carrier status identified through NBS to parents show that confusion regarding the information may lead to excessive worry about the infant's health, impaired bonding, and unnecessary medicalization of the child.[82,140,141] The term "non-disease" has been used to describe SCT identified through NBS, as the carrier state has few significant health implications for the infant yet can lead to adverse psychological effects for the infant's parent.[102] Feelings such as anxiety and depression have been reported by parents in response to learning that their child is a carrier for sickle cell or cystic fibrosis.[140–142]

Genetic testing may lead to the social harm of discrimination. This was a documented issue of early screening programs of the 1970s and 1980s, with cases of both job and insurance discrimination occurring due to SCT status.[10,103] Since this time, a number of federal laws have been developed to protect the confidentiality of personal health information and safeguard against employer discrimination and other forms of discrimination on the basis of genetic testing results. The Genetic Information Nondiscrimination Act (GINA) is a federal law passed in 2008, which dictates that genetic information cannot be used to determine eligibility or premiums for health insurance for individuals who do not show signs of the disease.[143] Genetic information includes both family health history and genetic test results. Under GINA, it is also illegal for employers to base hiring, firing, promotion, or pay on genetic information. There are limitations to the protection afforded by GINA, as it does not apply to life, disability, or long-term care insurance, nor does it

cover healthcare coverage provided by the government such as Tricare Military Insurance or the Veteran's Administration.[143]

With such legislature in place, concern for genetic discrimination may be diminished for current screening programs. When Acharya et at. administered in-person questionnaires to parents who had SCT themselves or had a child with SCT or SCD, none of the 47 respondents reported that they worried about discrimination related to SCT.[122] Additionally, no one expressed that they felt they had been rejected for a work position based on their SCT status. Two of the 47 respondents (4%) did report that they had experienced health insurance discrimination based on SCT status.

In spite of such findings, study participants from minority backgrounds have expressed fears about future insurability or abuse of genetic testing results. A 2007 interview-based study by Kass et al. provided grounds for this concern in relation to SCD and other single gene disorders.[144] Five hundred and ninety seven participants who were either affected with or at risk for a genetic or other chronic health condition or had a similarly affected child were surveyed about their experiences and beliefs regarding health insurance. Approximately 17% (99/597) of participants were affected with SCD or had a child affected with the condition. Individuals with SCD or cystic fibrosis (CF), another mendelian disorder, were twice as likely to report having been denied health insurance or offered it at a cost-prohibitive rate than individuals with conditions that were non-genetic in nature. Additionally, those with SCD were less likely to report that they had a choice when they were transitioning between insurance plans. These findings, although they may be explained by the fact that GINA does not apply to those already manifesting signs or symptoms of the condition, suggest that individuals receiving a genetic diagnosis through NBS may face genetic discrimination in health insurance.[143] Further studies are needed to clarify how this applies to a genetic diagnosis of SCT, which does not acutely impact health as does SCD.

2.2.5 Execution of Newborn Screening Programs for Sickle Cell Trait

Whether the potential risks and benefits of NBS for SCT are realized largely depends on how a program follows up on the positive screening results. Effective communication with families is central to ensuring that a program "does more good than harm:" That is, that the information is effectively imparted and utilized, and that any psychological and social complications are minimized.[142] The means by which the message is first disclosed to families warrants particular examination. Its impact may carry undue weight, as individuals appear to be better able to recall the first message compared to the information discussed later on in a counseling session.[142]

Disclosure of SCT status is often the responsibility of the infant's pediatrician or PCP. However, the ability of these providers to notify families of this information has been criticized.[145–147] One primary concern regards education. While the physician must help parents understand the reproductive and health implications of SCT, PCPs have been found to have a limited understanding about NBS and genetics in general.[148–150] In spite of this, counseling from general healthcare providers has been shown to contribute to increased patient knowledge. For example, in the study of Mayo-Gamble et al., women with SCT who reported having received hemoglobinopathy counseling from their PCP had significantly better scores on the SCD questionnaire than those who reported never having received counseling ($p < 0.05$).[131]

Results disclosure must also attend to the emotional needs of the family. Providing such support helps to minimize undue parental anxiety and contribute to the formation of an alliance between the PCP and parents. However, fault has been found with the psychological support provided by PCPs communicating SCT results, as they struggle to achieve a balance between concern and reassurance.[142] PCPs have also been shown to have difficulty identifying and responding to patient's emotions.[142,151,152] In the focus groups of Treadwell et al., participants

expressed a need for “compassion” and “love and nurturing” from physicians during SCT results disclosure.[120] These themes were not identified in the third focus group made up of providers, which identified education and community outreach as the primary keys to support. This discordance indicates that PCPs may not fully recognize and attend to the emotional needs of parents during disclosure of the SCT results.

Direct analysis of PCP’s communications with parents support this impression that trait status disclosures generally lack emotional support. When 116 randomly selected interactions between patients and PCPS were audiotaped and transcribed, PCPs were found to miss 79% of opportunities to positively respond to the patients’ emotional queues.[152] Similarly, when Bradford et al. assessed the social support behaviors of PCPs during SCT disclosures to standardized patients, they found a lack of emotional support.[153] In their analysis, Bradford et al. used a framework that defined five major categories of support. These were designated as either action-facilitating types of support (tangible aid support and information support) or nurturing types of support (esteem support, emotional support, and social network support).[154] In the 125 conversations analyzed, less than 10% featured emotional support, which was defined as the physician acknowledging the patient’s emotions and expressing empathy. Less than 2% of conversations provided esteem support, defined as engendering feelings of self-efficacy through encouragement. Physicians primarily used social network support and information support. The former, which can be described as expressing the intention to maintain an ongoing supportive alliance, was found in over half (61.6%, 77/125) of interactions; it primarily manifested as physicians emphasizing the ongoing follow-up care to be provided in future appointments. The availability of educational materials for parents was largely credited for the physician’s use of informational support, which was present in 38.4% (48/125) of their conversations. Bradford et al.

acknowledged the important limitation of their findings due to the study's artificial scenario yet discussed its unclear effect.[153] As their conversations were being evaluated, providers may have felt an additional drive to succeed. On the other hand, they may have been less motivated to provide support to individuals who were not their real patients.

Relying on PCPs to disclose NBS results and provide counseling for SCT may inadequately address the educational and psychological needs of families. Studies have demonstrated that when trait notification is facilitated by specialized healthcare provider such as a genetic counselor, it has positive effects on families both in terms of understanding as well as of reducing parental anxiety.[22,147,155,156] In spite of such findings, genetic counseling appears to be rarely utilized by those notified of their infant's positive NBS result for SCT when the services are offered. One assessment performed in northern California in the early 2000s found that less than 18% of families who were notified of their infant's trait status through the state's NBS program accepted free genetic counseling.[120] More aggressive follow-up of families for the NBS results may be needed to increase the proportion who see a genetic counselor for SCT. However such protocols have been criticized, as they may unduly magnify anxiety in families.[157]

In 2003, Kladny et al. addressed this critique by testing whether a flexible and accessible means of follow-up for SCT notification would increase utilization of genetic counseling services and be received positively by families.[24] Convenience for the families, as well as their general interest in receiving genetic counseling, were also considered. The intervention was carried out at the Pediatric Sickle Cell Clinic of CHP, which is contracted with the Pennsylvania Department of Health to follow-up on positive hemoglobinopathy and hemoglobinopathy trait NBS results in Western Pennsylvania.[23] In both this study and currently, a letter explaining the infant's positive screening result serves as the initial means of trait notification in the Pediatric Sickle Cell Clinic's

program. The letter, which is sent to the family within two weeks of the positive screen, is accompanied by an educational brochure regarding the specific hemoglobinopathy trait's health and reproductive implications. In the study by Kladny et al., notified families were also contacted on the telephone following receipt of the letter and offered the opportunity to schedule an in-person genetic counseling session at the Sickle Cell Clinic.[24] Parents who declined were offered the opportunity to speak with a board-certified genetic counselor over the telephone and also to be sent an educational video.

When three or more attempts made to contact each family, 53% percent of families (362/679) were reached by telephone by Kladny et al.[24] The majority (61%, 222/362) declined in-person genetic counseling. Among the 39% who did express interest, slightly under half (47%) successfully scheduled appointments. This resulted in 18% (66/362) of families who were reached by telephone secured genetic counseling appointments. The show-rate for these families was not reported.

A significantly greater proportion, 92% (333/362) agreed to receive telephone genetic counseling.[24] While no quantitative means of assessing of understanding gained through this session was performed, families confirmed verbally that they understood the information following the session. Additionally, Kladny et al. reported that all families were able to explain the general concepts back to the counselor prior to completion of the session.

Over one-quarter (27%, 99/362) of families contacted by Kladny et al. requested the educational video.[24] A seven question SCD knowledge questionnaire was administered to 43 of these mothers after they had watched the video. Relatively high knowledge scores were interpreted to indicate high efficacy of the video in imparting SCD knowledge, yet this conclusion is limited by the absence of a pre-video questionnaire to assess participants' prior knowledge. The

questionnaire found a relatively high understanding of autosomal inheritance in comparison to other studies, with 90.6% (39/43) of respondents agreeing that both parents had to have SCT in order for their child to be affected with SCD. The lowest average score was found in the question regarding the reproductive implications of HbC: "If one parent has sickle S trait and one parent has hemoglobin C trait, could they have a baby with disease?" Fifty-eight percent (25/43) of mothers answered this question correctly, while 16% answered incorrectly (7/43), and 26% (11/43) were unsure. This finding along with that of Boyd et al., where only 27% of African American women interviewed knew whether or not they were a carrier for HbC trait, supports an overall poorer understanding and awareness of variant hemoglobin traits beyond Sickle S trait.[119]

Kladny et al. also examined other parameters indicative of the impact of genetic counseling on the notified families. The emotional impact of the trait notification process was assessed by asking participants if they felt less anxious after watching the video. The majority (93%, 40/43) reported that they did feel less anxious.[24] For the remaining three individuals, it was not asked whether they felt more anxious, maintained their level of anxiety, or never felt anxious regarding their infant's SCT status. When sharing patterns of the health information were evaluated, 79% (34/43) of parents responded that they did intend to share their infant's SCT status with other family members. The study concluded that an intensive follow-up for SCT featuring multiple service modes increases utilization of genetic counseling for SCT, and that the majority of families are receptive to receiving these services by telephone.

To better understand the reception of the in-person genetic counseling for SCT identified through NBS, a follow-up study by Kladny et al. evaluated 114 of the 300 in-person genetic counseling sessions held at the Pediatric Sickle Cell Clinic from June 2003 to December 2009.[22] All of the 114 participants reported that the session had been educational, and 113 out of the 114

participants agreed that all of their questions had been answered by the session. Eight-two percent of participants stated that they felt less anxious after the session. Genetic counseling was also concluded to contribute to increased sharing of SCT status between reproductive partners. Specifically, 21% of participants reported that they discussed SCD with their partner prior to or during pregnancy. This rate significantly increased following the genetic counseling session, with 81% reporting that they would discuss this information with their partner. The reported 21% rate of sharing prior to genetic counseling is relatively low compared to other studies, yet the majority of these other studies report intentions of parents to discuss the information, rather than actualized sharing. Thus, the rate of 21% found by Kladny et al. may more accurately reflect true disclosure rates. In this case, the noted improvement in sharing rates, from 21% to 81%, derives from a comparison of past sharing (21%) to intended sharing (81%) and thus may be inflated. Additionally, it was not asked whether partners who did not discuss this information during pregnancy had been aware at that time that SCT was a chance for the pregnancy. Consistent with other studies, the great majority of respondents (91.2%, 104/114) expressed that they intended to share the infant's trait status with the infant him or herself at an older age.

In Pennsylvania, SCT notification remains a feature of the NBS program and continues to be facilitated by the mailing of a letter and informational brochure within two weeks of birth (Appendix B and Appendix C). The Pediatric Sickle Cell Clinic of CHP still offers in-person genetic counseling to families living within Region 6 of Western Pennsylvania. However, there is no longer the intensive follow-up as described by Kladny et al. due discontinuation of grant funding through HRSA.[22,24] Consequently, the letter serves as the only consistent form of communication to families about their infant's NBS results.

Genetic counseling for SCT is unavailable or under-utilized in many NBS programs.[21,73] A passive means of notification, such as through the mail, is the experience for a large proportion of parents in states whose programs directly notify parents.[21] While current literature has examined SCT notification facilitated by both PCPs and genetic counselors, it fails to directly address how trait notification through a mailing impacts families. By surveying parents who have received trait notification through this means, this study seeks to better characterize the harms and benefits of the NBS program for SCT experienced by a meaningful proportion of families. As this current study will draw from notified families living in the same regions previously recruited by Kladny et al., it will also allow for further evaluation of the additional services for trait notification that were the focus of these two previous studies.

This study will evaluate the effectiveness of the letter and informational brochure that is currently sent in Western Pennsylvania to notify families of their infant's positive screen for SCT in three categories: 1) disseminating relevant SCD knowledge 2) inducing parental anxiety, and 3) promoting sharing of the health information. As these three metrics characterize major benefits and harms of trait notification, this assessment will provide insight into the appropriateness of the public health program. This study plans to utilize what it learns from parents to revise the SCT notification letter sent in Western Pennsylvania. It may also potentially inform the NBS policies of Pennsylvania's and other states' programs.

3.0 MANUSCRIPT

3.1 INTRODUCTION

Sickle cell disease (SCD) refers to a group of inherited blood disorders characterized by a variant form of hemoglobin, whose sickling in the deoxygenated state contributes to severe pain, organ damage, and chronic anemia.[3,4] In the United States, SCD affects approximately 100,000 individuals.[34] SCD is an autosomal recessive disorder.[47] Its heterozygous carrier state, which is also known as sickle cell trait (SCT), is more prevalent in those with ancestry from malaria-endemic regions. This includes Southeast Asia, Indian, Africa, Latin American, and the Middle East and the Mediterranean. In the United States, the prevalence of SCT is highest among African Americans, where the carrier rate is approximately one in 12.[34] SCT is considered to be generally benign.[7] Its primary relevance to health is its reproductive risk, as individuals with SCT may have a child with SCD if their partner also carries a variant hemoglobin trait or disease.

Prior to the development of effective intervention, pneumococcal infection contributed to childhood mortality rates that were close to 30% for those with SCD in the United States.[70] This high mortality rate aggravated racial disparities in health that began gaining national attention in the 1960s.[64] In 1972, significant federal funding was devoted to SCD research and public health programs through the Sickle Cell Anemia Control Act.[76] This funding sponsored the multi-center, prospective Cooperative Study for Sickle Cell Disease (CSSCD) to study the natural history of SCD.[78] As one of the most influential projects to come from the CSSCD, the Penicillin Prophylaxis in Sickle Cell Disease (PROPS) trial was a double-blind, randomized control trial that demonstrated that penicillin prophylaxis provided significant protection against infection-related

morbidity and mortality in infants with SCD.[5] In response, the NIH sponsored a conference entitled "Newborn Screening for Sickle Cell Disease and Other Hemoglobinopathies," in 1987, after which a consensus statement was put forth recommending universal SCD screening of all newborns.[6] New York was the first state to adopt universal NBS for SCD, with subsequent uptake by other states. As of 2006, all 51 state and district programs include SCD in Newborn Screening (NBS).[2]

NBS is a state-based public health program that screens for congenital conditions in newborns so that those affected may receive treatment to improve their long-term health outcomes.[1] Relevant legislation is primarily made at the state-level, with each state determining its own screening panel as well as means for follow-up.[93] In 2006, in response to significant variability between states, the American College of Medical Genetics, as commission by the Maternal and Child Health Bureau under the Health Resources and Services Administration, published the Recommended Uniform Screening Panel (RUSP).[9] The RUSP provides guidance for the formation of states' screening panels. Hemoglobinopathies were included on the original RUSP. SCT is identified incidentally through the screening process, an in 1994, the Institute of Medicine published a report in support of sharing SCT status with parents. Their position stated that carrier status, even identified incidentally, is genetic information belonging to the infant, and by proxy to their parents.[8] However, states continue to vary significantly in their policies regarding SCT notification. In a survey of NBS programs carried out in 2008, approximately one third of states reported means for notifying parents of positive SCT screening results.[21]

No universally accepted policy currently exists regarding parental notification of SCT identified through NBS.[21,73,107] A number of ethical, as well as evidence-based systems, have been developed to guide the determination of the appropriateness of screening programs in public health.[111,112,115] In general, a public health program's potential benefits may be weighed against its

potential risks. Arguments for reporting SCT focus on the reproductive implications of the information, both for the newborn and their parents.[8,158] In particular, knowledge deficits regarding SCD and personal SCT status persist among at-risk communities and also are a stated concern of these communities.[17,18,118–120,122] If increased awareness and understanding of SCT can be achieved through NBS, this may promote informed reproductive choice.

A number of potential risks for SCT notification also exist. These include the possibility of stigmatization, discrimination, and adverse psychological impact.[103,133,135] Many of these have been borne out in past screening programs for SCD and have the potential to exacerbate, rather than improve, health disparities if screening is haphazardly implemented. In the 1970s, population-based screening programs for SCD failed to effectively communicate the generally benign nature of SCT and distinguish it from SCD.[12,103] The resulting confusion perpetuated fear, stigma, and discrimination.[10,11,13,49] These programs were also criticized for coercive reproductive counseling, rather than promoting informed choice and autonomy.[159] NBS notification for carrier status in current programs has been found to result in emotional distress and anxiety as it regards both sickle cell and cystic fibrosis.[135,140,147] The risk for these potential psychological harms caused by SCT notification must be considered in respect to proposed benefits in the program's implementation.

Effective trait notification must adequately impart SCT awareness and knowledge to relevant stakeholders without causing undue emotional distress. Previous studies have demonstrated that genetic counseling following SCT notification is received positively by families and promotes understanding and communication among family members [22,24,147,155,156] However, resources limit the availability of genetic counselors' and other specialists' services.[21] Follow-up more often falls to PCPs, who have been found to be inadequately prepared for this role.[149,150,153,160]

Even when discussion with a specialized healthcare provider is available, it is not routinely sought out by families following trait notification.[22,24]

A common strategy of NBS programs is to notify families of their infant's positive screen for SCT through a letter. In the Pennsylvania NBS program, families are sent a letter and educational brochure within two weeks of the hemoglobinopathy referral center's notification of the result.[106] The mailing, which is specific to the particular hemoglobin trait identified, also includes a telephone number for the Pediatric Sickle Cell Program of CHP. The Pediatric Sickle Cell Program receives funding by the state's Department of Health to send the notification letters for positive NBS results for hemoglobin variant traits, as well as performs follow up for hemoglobinopathy results. The program also offers genetic counseling to families whose infant screens positive for SCT; however, the great majority of families do not attend an in-person genetic counseling session.

This study seeks to evaluate the ability of the current SCT notification letter sent in Western Pennsylvania to covey knowledge about the reproductive and health implications of SCD, as well as to promote emotional wellbeing and communication of the results to appropriate family members and health care providers. The literature, while it has explored SCT results disclosure by genetic counselors and PCPs, inadequately addresses the effects of trait notification facilitated by a mailed letter. As the trait notification letter is the only follow-up received by many families regarding the NBS results, a study of its impact in absence of follow-up counseling and educational services is particularly warranted.[12] The results of this study have the potential to inform policy regarding SCT disclosure for both Pennsylvania's NBS program as well as other states'.

3.2 METHODS

The University of Pittsburgh Institutional Review Board (IRB) approved this study under IRB # PRO 18060433 (Appendix A).

3.2.1 Participant Selection

This study was conducted through the Pediatric Sickle Cell Clinic at CHP. The clinic is one of six regional specialty centers that are contracted with the Pennsylvania Department of Health and receives funding through the Maternal and Child Health Bureau under HRSA to follow-up on positive NBS results for hemoglobinopathies and hemoglobinopathy traits.[106] The Pediatric Sickle Cell Clinic covers Region 6, which includes 19 counties in the western portion of the state (Figure 1).

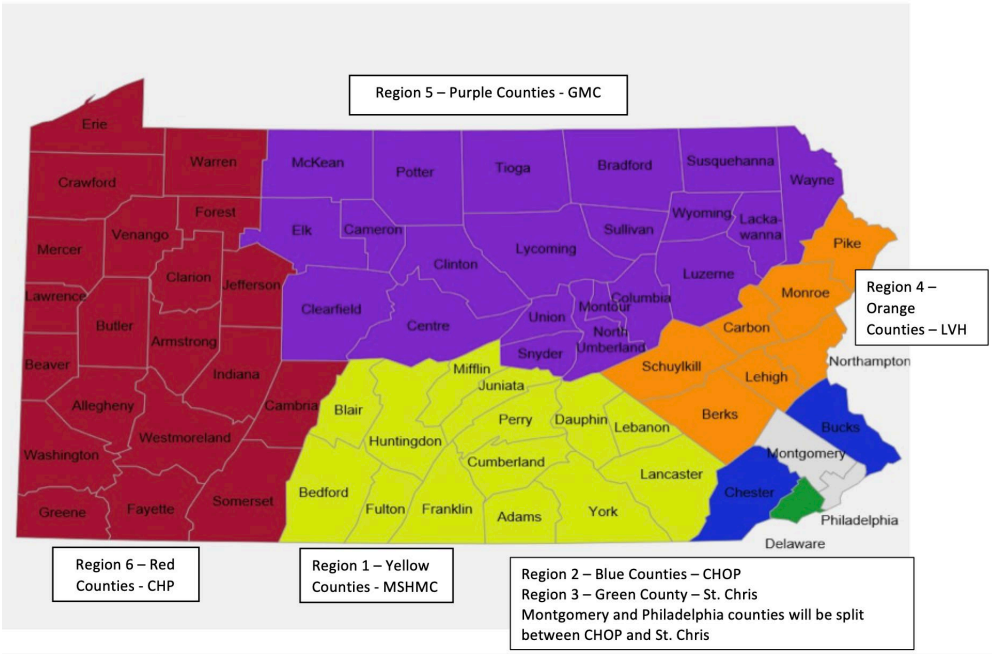


Figure 1. Division of Newborn Screening and Genetics Hemoglobin Trait Map

As one of two laboratories contracted with the Pennsylvania Department of Health to perform the biochemical screening for NBS, PerkinElmer Genetics, Inc. tests for hemoglobinopathies. The laboratory maintains a database of infants who have screened positive for a hemoglobinopathy or hemoglobin variant trait, which can be accessed by region. The names and demographic information of infants who screen positive for a variant hemoglobinopathy trait within Region 6 are queried every two weeks and entered into the Sickle Cell Database (SCDB), which is an electronic database saved on a secure University of Pittsburgh Medical Center (UPMC) server. The SCDB contains information on all active and past patients seen by the Pediatric Sickle Cell Clinic since 1999, as well as on all infants who have screened positive for a hemoglobinopathy or hemoglobinopathy trait through NBS since this date.

In October 2018, the SCDB was queried for the names of all infants who had received a positive screen for Sickle S trait or HbC trait in Region 6 from four to 56 weeks prior to this date. The study's population was limited to these variant hemoglobin traits, as they are the most common structural hemoglobin variants that contribute to SCD in the United States. Thalassemia traits were excluded because their inheritance and clinical implications are more complex.[4,34]

For each infant identified from the SCDB, a number of additional demographics were also retrieved. This included the mother's surname, date of birth, sex, filter paper number, date of specimen collection, hemoglobinopathy profile, birth hospital, mother's first and last name, mother's address, mother's phone number, physician's name, and physician's phone number. In the case that a mother was represented by more than one entry, either due to multiple births or a repeated NBS screen on the same infant, only one entry was retained. This was done to ensure that each family was sent only one survey. Each entry was assigned a unique number in sequential order, and surveys were coded in a corresponding fashion. This allowed for survey responses from

returned mail surveys to be matched to the corresponding notified family. This collection of coded demographic information served as the codebook and was stored on a secure server maintained by CHP.

3.2.2 Mailed Surveys

Each mailing was comprised of 1) a waiver for signed informed consent, 2) a generic copy of the NBS trait notification letter for "Baby Male Doe" with date of birth March 1, 2017, 3) a copy of the informational brochure provided with the original trait notification, 4) the 20-question survey, and 5) a paid-return envelope addressed to the Pediatric Sickle Cell Program of CHP (Appendix B-Appendix E). The letter, brochure, and survey were specific to the variant hemoglobin trait (Sickle S trait or HbC trait) identified through the screening. The letter was addressed to the mother of the infant specified by the NBS bloodspot, as this is how the original trait notification letters are addressed. Respondents were asked to confirm that they were over 18 years of age in order to participate in the study. No compensation was offered. The survey introduction noted that one goal of the study was to improve the current notification letter.

The surveys were designed to evaluate three potential consequences of trait notification: 1) general SCD knowledge (Knowledge), 2) emotional impact on parents (Anxiety), and 3) disclosure of infant's positive SCT status with relevant family members and healthcare providers (Sharing).

The eight-question SCD knowledge questionnaire developed for Part 1 ("Knowledge") was adapted from the questionnaire administered by Kladny et al. to families following an SCD educational video.[22,24] The first seven questions were identical to this previous survey, except it specified the letter, rather than the video, in one question. Participants were provided with three checkboxes (Yes, No, and Unsure) on the mail survey to record each answer. An additional

question was added to the end of the knowledge questionnaire, which asked the specific chance of having a baby affected with SCD if both parents had SCT. For this question, respondents were provided with the answer choices of 0%, 25%, 50%, 100%, and Unsure.

Part Two of the mail survey examined the psychological impact of the letter, focusing on anxiety. The Patient-Reported Outcomes Measurement Information System (PROMIS) Short Form 8a Scale of Anxiety was adapted for this aim. PROMIS is a validated survey tool developed by the NIH to measure emotional distress through self-report with a high degree of reliability and precision.[161] The PROMIS Short Form 8a for Anxiety may be used in the general public and uses universal measures of the symptoms of anxiety: fear (fearfulness, panic), anxious misery (worry, dread), hyper-arousal (tension, nervousness, restlessness), and somatic symptoms (racing heart, dizziness). Responses range from 1 ("Never") to 5 ("Always"). Scores are transformed to compare to a normalized curve of scores derived from the general American public with a mean of 50 and a standard deviation of 10. For the purpose of this study, participants were asked if they experienced the specified symptoms of anxiety in response to learning about their infant's positive SCT status. The time frame of the PROMIS survey was modified from "the past week" to assess participants' anxiety since receiving the trait notification letter.

In the third part of the survey, respondents were asked about the individuals with whom they had already shared or planned share their infant's trait status. Four individuals were specified: the respondent's partner, the infant's doctor, the respondent's own doctor, and the infant when he or she was older. The choices provided were Yes, No, and Unsure.

The final part of the survey asked for additional thoughts or feelings about the notification letter. A blank space under the question was left for participants' responses.

3.2.3 Phone Surveys

Two months following the mailing of the surveys, telephone calls were initiated to administer the survey to parents who had not returned the mailed survey. The calls were made on weekdays during the months of December and January, between the hours of 9am and 6pm. At least two call attempts were made for every working number in the codebook. No voicemails were left, but a voicemail was counted as one call attempt. Calls and telephone survey responses were recorded on individual tabs of the codebook.

Two genetic counseling Masters students, who had previous experience in the Sickle Cell clinic and training by a boarded hematologist, administered the telephone surveys A telephone script along with training of one interviewer by the other ensured consistency (Appendix F). Parents were first asked if they recalled receiving a letter about SCT a few months to one year ago. Those who reported that they did not recall receiving the letter were asked if their pediatrician or other provider had talked to them about their infant's NBS result for SCT. If they were aware of their infant's positive screen, the parents were assured that the call did not regard their child's health and was for a research study. As the survey sought to evaluate the mail notification process, individuals who did not report recalling the letter were noted in the codebook but were not eligible to participate in the survey. For parents who neither remembered receiving the letter nor expressed awareness of their infant's positive screen, the interviewer disclosed the positive screening result for SCT. The parent was assured that their infant was healthy and did not have SCD. SCT was explained as a generally benign carrier status with normal lifespan and normal fertility. Its implications for reproduction, both for the child as well as for the parents, were discussed, along with the potential for the health complications of traumatic hyphema, hematuria, and a mildly elevated risk for rhabdomyolysis in the setting of exertional heat illness. Parents were given the

opportunity to ask questions or follow-up with a board-certified genetic counselor or hematologist if they desired. The number to the Pediatric Sickle Cell Program that was included NBS letter was also given to them at the end of the call in the case they thought of questions at a later time.

Parents who confirmed receipt of the original trait letter and/or the mailed survey were offered the opportunity to participate in the survey over the telephone. The survey took between five to ten minutes to administer, with additional time for follow-up questions and education as needed. The first eight questions, which were the knowledge-based questions, were administered verbatim from the mail survey. Mothers were encouraged to answer "yes" or "no" to the questions, but an answer of "unsure" was accepted if they refused. No correction or confirmation of answers was given until the completion of the entire survey.

Participants were informed that for the second half of the survey, there were no right or wrong answers, as the questions concerned their emotions and opinions about the letter's information. The PROMIS survey, which was used to assess anxiety in the mail survey, is not designed to be administered over the telephone. Thus, a single question was asked for this section of the telephone survey. The interviewer asked participants if they had felt "nervous, fearful, or anxious" about their infant's SCT status since receiving the notification letter. Responses were recorded as either "yes" or "no." Any reply other than "no" or "not really" was coded as "yes." Elaboration on the question was transcribed with the participant's survey responses.

For the last section (Sharing), parents were again reminded that there were no right or wrong answers in order to encourage honest reporting of with whom they had shared or planned to share the letter's information. Participants were again encouraged to respond with "yes" or "no", but an answer of "unsure" was accepted. At the end of the survey, participants were asked if they

had any additional thoughts or questions regarding the screening letter or information that was discussed. With the participant's permission, these remarks were transcribed.

Following completion of the survey, the interviewer asked the participant for permission to review the answers to the knowledge questions. Additional information was also given if the participant expressed confusion or asked further questions. If the information requested was outside of the comfort level of the interviewers to impart, participants were given the number of the Hemoglobinopathy RN Coordinator, who is trained to counsel parents regarding SCT NBS results, and referred to the Hematology clinic as needed.

3.2.4 Data Analysis

All responses to the mail and telephone surveys were recorded in Microsoft Excel. For Part 1 (Knowledge) and Part 3 (Sharing), descriptive statistics were calculated for the mail and telephone survey responses separately, as well as combined. Descriptive statistics were also calculated for the responses to the telephone survey for Part 2 (Anxiety). For Part 2 of the mail survey, which used the adaptation of the PROMIS short form, responses were summed and scored as instructed by PROMIS Anxiety Scoring Manual. The mean of the participants' raw scores was transformed into a T-score, with a mean of 50 and a standard deviation of 10, using the provided score conversion table (Appendix G).

R Studio for Mac Version 1.1.456 was used for statistical tests. Specifically, chi-squared analysis was performed to compare the knowledge scores of this survey with those of Kladny et al.[24]

3.3 RESULTS

3.3.1 Survey Responses

Four hundred and forty-one positive NBS screening results for Sickle S trait and HbC trait from Region 6 were downloaded from the SCDB using a one-year time span ranging from four to 56 weeks prior to the date the data of download. Following the removal of seven entries, which represented either multiple births or repeat screens for the same infant, results for 434 unique mothers remained (Figure 2). Three hundred twenty-nine (75.8%) of these were for Sickle S trait and 105 (24.2%) were for HbC trait. The majority of mothers (72.6%) reported a home address in Allegheny County, which is the county where the Pediatric Sickle Cell Program of CHP is located. The second highest representation, with 12.2% of mothers, came from Erie County, which is approximately 120 miles from the clinic. Less than 10% representation came from the remaining 11 counties.

Over the five weeks after mailing out the surveys, thirteen (3.0%) completed mail surveys were returned to the Pediatric Sickle Cell Program. An additional 40 (9.2%) surveys were mailed back as undeliverable. This represents a mail response rate of 3.3% (13/394).

Two months after the surveys had been mailed out to families, telephone calls were made to all parents who had not returned a completed mail survey. Of the 421 numbers attempted, 98 (23.3%) were no longer in service. A voicemail or busy tone was reached on both call attempts for 145 (34.4%) of numbers. For the remaining 178 (42.8%) telephone numbers, an individual was reached by telephone. The interviewer was informed that the number was incorrect or that the mother could no longer be reached at that number for 24 (5.7% total) of these telephone numbers. Fourteen of the parents who were reached were ineligible for the survey, as they either did not

speak sufficient English (n = 2, 0.5%) or reported that they did not recall receiving the trait notification letter originally or with the survey (n = 12, 2.9%). In three of these latter cases, the parent also reported not knowing about their infant's positive NBS result. After confirmation that their demographic information matched those of the NBS results reported on the NBS bloodspot, the results were disclosed over the telephone. Fifty-nine (14.0%) of the parents who were contacted over the telephone either declined participating in the survey or asked to be called back but could not be reached at a later time. Eighty-one (19.2%) of parents contacted by telephone completed the survey.

By matching the mailed surveys that had been returned as undeliverable to the corresponding parent on the call log, it was found that the interviewers had reached sixteen of these intended recipients. Only one parent reported that she did not recall receiving the original mailed notification letter. Among the other 15 parents who were reached by telephone, five consented for the survey and 10 declined the survey. The remaining 24 parents whose mail survey was returned as undeliverable could also not be reached by telephone: three telephone numbers were reported to be wrong numbers, eight were disconnected, and 13 went to voicemail on both call attempts.

Subtracting out the 281 total telephone numbers dialed where the parent could not be reached over the telephone or were ineligible, the response rate for calling was 57.8% (81/140). This resulted in a total of 94 completed mail and telephone surveys, representing 21.7% (94/434) of parents whose infant screened positive for Sickle S or HbC trait within Region 6 in the past year.

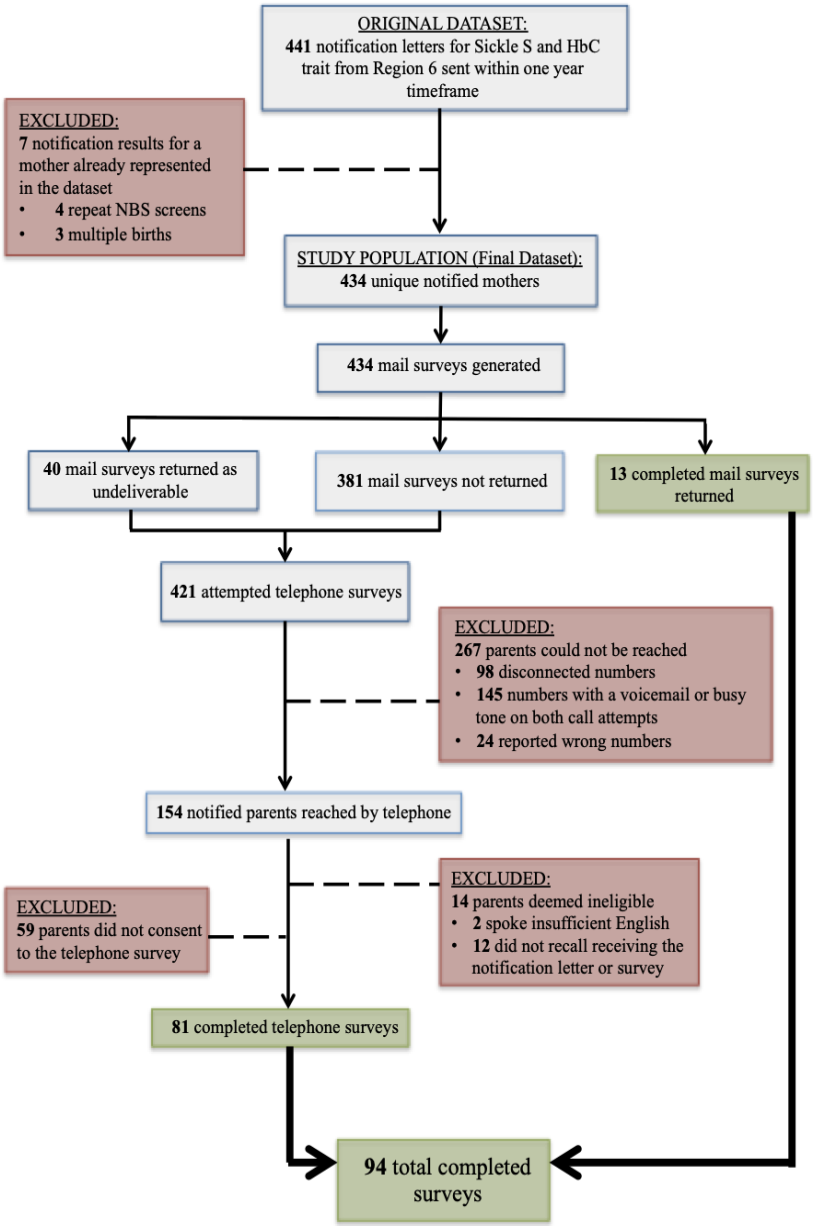


Figure 2. Flowchart of Survey Administration

3.3.2 Aim 1: Sickle Cell Knowledge

On the first section of the survey (Knowledge), the mean total correct score was 70.5%. By mail, the mean total score was 75% (n = 13) and by telephone, it was 69.8% (n = 81). Appendix H contains a breakdown of correct response rate by survey type.

Over 95% of parents reported that the notification letter clearly distinguished SCT from SCD (Table 6, *Question 1*). However, 28.7% of participants responded incorrectly that SCT could develop into SCD, or that they were uncertain whether it could, indicating confusion over the distinction between SCD and its carrier state (*Question 2*).

The highest correct response rate was obtained for the question regarding whether or not SCD is contagious. All those surveyed through both mail and the telephone responded that SCD could not be "caught like a cold" (*Question 7*). Thus, participants appeared to generally appreciate the congenital nature of SCD. There was less understanding regarding how SCD is inherited, with only 63% of survey participants correctly answering that both parents need to possess an abnormal hemoglobin trait for their baby to be affected with SCD (*Question 3*). Scores were lower in the context of how HbC trait contributed to reproductive risk. When parents were asked whether a couple in which one individual has Sickle S trait and the other individual has HbC trait could have a child with SCD, just over half of respondents (53.2%) answered correctly (*Question 4*). When this question was broken down by NBS result, significantly higher scores were found among those mothers whose infant screened positive for HbC trait, compared to those for Sickle S trait: 71.4% (20/28) versus 45.5% (30/66), $p = 0.02$.

Responses to two additional questions further underline the lack of clarity among surveyed parents regarding the way SCD is inherited. First, over one quarter (25.6%) of parents responded that their brother or sister could *not* also have SCT if they themselves did (*Question 5*). When participants were asked to select the percentage chance that a child would be born with SCD if born their parents had SCT, the correct percentage (25%) was given by 14.9% of mothers. This resulted in the lowest average score among questions in the knowledge section of the survey, although importantly, this was not a true/false question but presented four options for a response.

The most common response given by participants was 50%, which represented 51.1% of total responses. This was followed by 25.5% of parents who responded that if both parents had SCT, their child would have a 100% chance of having SCD.

Table 6. Knowledge Questionnaire Scores

Question *(Answer)*	**Percent Correct**
1. Did the letter make it clear that there is a difference between sickle cell trait and sickle cell disease? This is not a question that can be answered correctly or incorrectly (*Yes*)	95.20%
2. Can a child with sickle cell trait ever develop sickle cell disease? *(No)*	71.30%
3. Do both parents have to have sickle cell trait for a baby to be born with sickle cell disease *(Yes)*	63.80%
4. If one parent has sickle S trait and one parent has hemoglobin C trait, could they have a baby with disease? *(Yes)*	53.20%
5. If you have sickle cell trait, could your brother or sister also have sickle cell trait? *(Yes)*	74.50%
6. Can you choose which genes are passed onto your children? *(No)*	93.60%
7. Can you "catch" sickle cell disease like a cold? *(No)*	100%
8. If both parents have sickle cell trait, what is the chance that their child will have sickle cell disease? *(25%)*	14.90%
Average Score	**70.50%**

3.3.3 Aim 2: Anxiety

Potential anxiety elicited by the notification letter was measured through two different methods depending on survey format. The eight-question PROMIS short form was used to measure anxiety and emotional distress in the mail surveys. All 13 mail survey respondents completely filled out the PROMIS form. The mean raw score was 13.5. Using the conversion table for the Adult Anxiety short form and rounding up, this corresponds to a T-score of 50.8 with a standard error of 2.2 (Appendix G). This value is not significantly different from the general population mean of 50.0, suggesting that on average, the mail survey participants did not experience increased anxiety or emotional distress due to carrier identification.

Individual scores for the mailed surey PROMIS scores were not normally distributed and indicated that a proportion of parents were made anxious by the notification, however. A density plot of scores shows a bimodal distribution (Figure 3). Approximately one-third (30.7%, 4/13) of participants' rounded individual scores were at least one standard deviation above the general population mean (60.0 or greater). This suggests that these parents experienced a significant level of anxiety from the trait notification. The two mail survey participants who provided feedback in the final section of the survey emphasized an initial negative reaction to the letter:

"I checked sometimes in those 3 boxes because that is how I felt when I first found out she had the trait. But now that I learned about it and read about it I feel much better."

"The letter made me feel generally uncertain…about the present and the future. I could tell it was intended as notification and tried to reassure me that nothing is wrong, but it is still very intimidating to be contacted by the Hematology/Oncology department of Children's Hospital..."

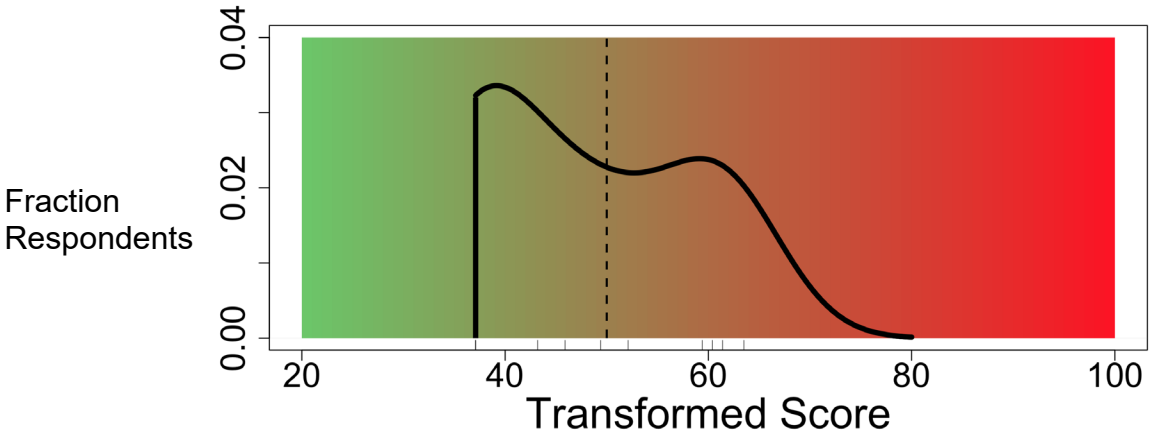


Figure 3. Range of Transformed PROMIS Scores (n = 13)

In the telephone surveys, parents were asked if they felt "nervous, fearful, or anxious" about their baby's positive screen for SCT in the time since receiving the letter. The rate of anxiety demonstrated by these responses was similar to that observed through the mail, in spite of the different survey modes and measurement tools. Specifically, just under one-third (30.9%, 25/81) of the eighty-one telephone survey respondents confirmed they had been emotionally distressed by the letter, compared to 30.7% (4/13) of the mail survey recipients.

While no formal qualitative analysis was performed on the additional remarks made by the telephone survey participants, their elaboration provided additional insight into their emotional reaction to the letter (Appendix I). Parents who denied experiencing any anxiety commonly evoked personal experiences with SCT that were in line with its generally minimal effect on health. The reflections of those who did report a negative reaction commonly included a feeling of fear or nervousness from receiving a letter from CHP regarding their infant. Often, it seemed this reaction had subsided within a few days to a week.

Many parents discussed how they had grown reassured through gaining better understanding of the letter's information. Highlighting the relevancy of the knowledge sections' first two questions, which concerned the distinction between SCT and SCD, parents' anxiety seemed to be often relieved by clarifying that the letter regarded trait rather than SCD. Parents reported that they sought clarification through re-reading the mailing or through speaking with a health care provider, who was primarily their infant's PCP, or a family member. A small, but not quantified number of parents did speak of lingering worry about their child when he or she was ready to have children, or fears that he or she would not be able to do sports.

3.3.4 Aim 3: Sharing Patterns

Both survey modes demonstrated a relatively high degree of anticipated sharing of the letter's information. Over 95% of participants expressed that they had discussed or planned to discuss their child's positive SCT status with the family members named by the survey (Table 7). Specifically, 96.5% of parents reported feeling comfortable discussing the information with their reproductive partner, and 98.9% planned to share their infant's trait status with him or her at an older age.

A smaller proportion, yet still the majority of parents, reported that they would or had already discussed this information with healthcare providers: 90.4% with their child's physician and 71.3% with their own physician. Telephone respondents who answered that they had not and did not plan on discussing SCT with their own physician often indicated that this was because it was their partner who was responsible for their infant having SCT. In these cases, it was not clarified whether either partner had received hemoglobinopathy testing to determine that this

report was accurate and also that respondent was not also a carrier of a variant hemoglobinopathy trait.

Table 7. Reported Disclosure Patterns

Have you or do you plan on sharing the letter's information with your:	Yes	No	Unsure
Partner	**96.8%**	3.2%	0%
Child	**98.9%**	0%	1.1%
Child's Doctor	**90.4%**	6.4%	3.2%
Own Doctor	**71.3%**	25.5%	3.2%

3.4 DISCUSSION

This study examined the impact of SCT identification in an NBS program which directly notifies families through a letter. Parents who had received the letter for either Sickle S or HbC trait within the past year were surveyed through the mail and over the telephone. The survey addressed the three specific areas of 1) sickle cell knowledge, 2) emotional distress elicited by the notification letter, and 3) anticipated disclosure of its information, as these characterize potential benefits and harms of trait notification.

3.4.1 Aim 1: Sickle Cell Knowledge

Disclosing positive NBS results for SCT may promote the understanding of genetic information that has great relevancy for reproductive decisions. An increased awareness of this information has been called for by the communities most directly impacted by SCD, and is also outlined by current clinical and prenatal guidelines.[14–16,19,20,120] This study aimed to evaluate the effectiveness of one NBS program at disseminating this knowledge to at-risk families.

Answers to the knowledge assessment's first two questions suggest that the current trait notification letter fails to clarify the health consequences of SCT for a substantial proportion of notified parents. While over 95% of participants stated that the notification letter made the difference between SCT and SCD clear, more than one-quarter (28.7%) reported that the carrier state could develop into SCD. Previous studies, which have similarly assessed understanding gained through trait notification facilitated by a letter, have also found high rates of confusion among its population regarding the distinction between SCD and SCT. In one such study, Lang et al. surveyed mothers who had first been notified of their infant's positive screen for Sickle S trait by an informational mailing sent through the Illinois NBS program. Forty-four percent of mothers answered the equivalent question incorrectly, replying that "over time, carriers of SCD (people with SCT) can develop SCD." Forty-one percent of mothers responded that "people who are carriers of SCD (people with SCT) have a mild form of SCD," which is also false.[17]

While this current study found a lower rate of misunderstanding between SCT and SCD than was found in mothers similarly notified through the Illinois NBS program. its finding that over one-fourth of parents believe that SCT could turn into SCD is particularly concerning among individuals who have just learned of their newborn's positive screen for SCT.[17] An inability to distinguish SCD from its generally benign carrier state may contribute to an erroneous view of

their infant's poor health and increase anxiety. An exaggerated perception of the health consequences of having SCT appears to persist among African American communities.[120,122,136] This may be attributed to both historical and contemporary events. For four decades following James Herrick's initial publication of SCD, SCT was thought to be a more mild form of the condition.[47,65] The initials sickle cell screening programs propagated this misconception among the general public.[13] Contemporary SCT screening programs of some military branches and the NCAA have also been criticized for over-emphasizing the personal health implications of SCT, thereby conflating SCT with a more clinically significant condition.[58,61,62] This study's findings indicate that the current trait notification process may also inadequately establish the difference between SCD and SCT for a meaningful proportion of parents of whose infants screened positive for SCT. This is one potential harm of the program.

The reproductive implications of SCT motivate programs to share the screening results with families. However, responses to this study's survey demonstrate that the current letter does not adequately impart to parents how having SCT may lead to having a child with SCD (Table 6; *Questions 3, 4,* and *8*). This is consistent with other similar knowledge assessments, which have found that in spite of a relatively high appreciation for the condition's hereditary nature, there is poorer understanding of its specific mode of inheritance (Table 5). Over one-third (36.2%) of this current study's participants did not recognize that both parents must have SCT for their child to have SCD. This incorrect response rate is similar to that found by Lang et al., who found that 33% of notified Illinois mothers incorrectly confirmed that "you can be a carrier of SCD (have SCT) even if neither parent has disease or trait." In responding to this question over the telephone, a number of this study's parents articulated the common misconception that SCD "skips generations."

Such confusion over how SCD is inherited was further highlighted by the last question of this survey's knowledge assessment, which specifically inquired about the reproductive risks associated with autosomal recessive inheritance. This question received the lowest scores of Part One (Knowledge). A greater proportion of participants (25.5%) responded that a carrier couple would have a 100% chance of having a child affected with SCD than those who gave the correct chance of 25% (15%). While reviewing the answers, a number of participants expressed disbelief that the chance was "only 25%." In light of studies that have largely found their African American participants have a low perceived personal risk of having a child with SCT, this finding is particularly surprising.[16,17,120,122] In particular, it contrasts those of Gustafson et al., where a higher perceived personal susceptibility was found to significantly correlate with an understanding of autosomal recessive inheritance.[121] This may indicate that a lack of understanding of the inheritance pattern of SCD is not the greatest barrier to accurate risk perception. Other factors, which likely correlate with a specific understanding of the inheritance pattern, may more strongly contribute to accurate risk perception. An awareness of one's partner's and one's own trait status, an appreciation for the high prevalence of SCT, and having personal or familial experience with sickle cell have also been found to influence reproductive decision making in relation to SCD. While this study did not evaluate parents' perceived risk for having a child with SCD, responses to this final question of the knowledge assessment suggest that further evaluation is needed to clarify what information should be prioritized in order to promote accurate risk perception in this population.

This study found a mean knowledge score of 70.5%. While this is comparable to scores deemed to be "insufficient" by other study authors, score interpretation is subjective in nature.[119,122] Thus, this measurement's primary utility is in its ability to be compared with other

populations to evaluate the effect of interventions. In a previous study by Kladny et al., the same knowledge questionnaire used in this study was administered to a similar population who also received additional educational services.[24] Parents living in Region 6 of western Pennsylvania who had been notified through the mail of their infant's NBS screen for SCT were surveyed about their knowledge of sickle cell after watching an information video. The video was concluded to promote greater understanding, with all but two families surveyed (95%, 41/43) reporting that the video had provided them with additional information about SCT that they had not known previously. However, without a pre-video assessment, Kladny et al. was unable to determine what knowledge was specifically gained through the video. As this current study utilized the same set of questions to assess the SCD knowledge of notified parents living in Region 6 who had only received the notification letter, it can provide further insight into the impact of educational services following trait notification.

In comparing the results of this current survey to those of Kladny et al., additional learning does appear to have been facilitated by the educational services (Table 8). Significantly higher scores were achieved for three of the six knowledge questions asked of both groups by the population of parents who had watched the video ($p < 0.05$).[24] For those questions for which the additional education did not correspond to significantly higher scores, the scores were greater than 90% in both groups. This suggest that there is an opportunity to further increase SCD-related knowledge after families are initially notified of the NBS results through the mail. However, other differences may exist between these two groups, such as the motivation to watch the video, to account for the deviations in scores. Support for additional services following trait notification to increase understanding of SCD is provided by other studies. Namely, Lang et al. administered both pre- and post- intervention knowledge questionnaire to their population of mothers in the Chicago,

Illinois area, who had also been notified of their child's positive NBS screen for SCT through a mailing. Participants who attended an in-person sickle cell educational program significantly improved their average scores (69% versus 76%, $p < 0.01$). Following the program, significantly higher correct response rates were also found for three of the questions previously discussed: 1) *Over time, carriers of SCD (people with SCT) can develop SCD*, 2) *People who are carriers of SCD (people with SCT) have a mild form of SCD*, and 3) *You can be a carrier of SCD (have SCT) even if neither parent has disease or trait* ($p < 0.05$).

Further understanding of SCT has also been identified as a need by notified families who seek out additional services after receiving the NBS letter for SCT. When Kladny et al. surveyed mothers who attended in-person genetic counseling sessions following trait notification through the mail, the majority (52%) reported that their main motivation for genetic counseling was a desire to obtain more information.[22] Following this was 22% who reported it was due to their physician's recommendation, and then 13% who responded that it was for "peace of mind."

In the context of these two earlier studies of Kladny et al., the first of which assessed SCD knowledge of families who had received additional educational services following the notification letter and the second of which surveyed mothers for their motivation to seek out in-person genetic counseling regarding SCT, as well as those of Lang et al., results from the first part of this study's survey indicate that trait notification through the current letter alone inadequately addresses the educational needs of families.[17,22,24] Additional services appear to increase understanding of the health and reproductive implications of SCT following notification by mail; greater understanding of SCT also appears to be the primary motivation of a large proportion of families who seek out follow-up counseling services. Ensuring families access to such resources will allow for the benefits of the NBS program to be more fully realized. Further evaluation is needed to clarify what

information most significantly influences reproductive decisions in this population and how to most effectively execute these services in Western Pennsylvania specifically.

Table 8. Comparison of SCD Knowledge Surveys

Question (*Answer)*	Trait Letter Only (n = 94)	Trait Letter and Educational Video[24] (n = 43)
1. Did the letter/video make it clear that there is a difference between sickle cell trait and sickle cell disease? This is not a question that can be answered correctly or incorrectly *(Yes)*	95%	93%
2. Can a child with sickle cell trait ever develop sickle cell disease? *(No)*	71%	91%*
3. Do both parents have to have sickle cell trait for a baby to be born with sickle cell disease *(Yes)*	64%	91%*
4. If one parent has sickle S trait and one parent has hemoglobin C trait, could they have a baby with disease? *(Yes)*	53%	58%
5. If you have sickle cell trait, could your brother or sister also have sickle cell trait? *(Yes)*	75%	91%*
6. Can you choose which genes are passed onto your children? *(No)*	94%	95%
7. Can you "catch" sickle cell disease like a cold? *(No)*	100%	93%

** Statistically significant increase in score ($p < 0.05$)*

3.4.2 Aim 2: Anxiety

Responses to the first section of this study's survey (Knowledge) demonstrate that the current notification letter fails to fully clarify the distinction between SCT and SCD among parents whose infant screens positive for SCT in Western Pennsylvania. Confusion about the health risks of SCT was widely propagated by the nation's earliest SCD screening programs; this contributed to undue anxiety among those screened and lead to programs' early termination.[10–13] [2] In current NBS programs, parental anxiety remains a concern of carrier identification, which occurs not only for SCD, but for other conditions such as cystic fibroris..[49,140,141] In light of the minimal health implications of SCT, any emotional distress caused through notification of families is particularly pertinent to the program as a potential harm.

Despite using different measurement tools, both the mail and telephone surveys found that approximately one-third of notified parents were made anxious by the NBS mailing (30.7% and 30.9%, respectively). Participants' feedback often suggested that their anxiety was elicited by learning this information about their infant's health that they may not fully comprehend or by receiving an official mailing from CHP about their newborn. Thus, their elaborations emphasized an initial negative reaction to the letter. Both survey methods measured a sustained emotional response to the letter, however, which suggests that the anxiety reported by just under one third of notified parents persists. This conclusion is supported by findings of Lang et al. who surveyed mothers notified through mail of their infants' positive screen for SCT through the Illinois NBS program: 24% (15/62) of mothers who had received the notification mailing more than one month prior to completing survey reported that they still thought about their infant's positive trait status at least once a week.[17]

Although no qualitative analysis was performed on participants' commentary, several observations made by those administering the survey provide further insight into the emotional reaction of notified parents. Those surveyed over the telephone often reported that their anxiety began to diminish once they felt they had gained a clearer understanding of the letter's information. As many of this study's telephone participants reported re-reading the letter to feel reassured, the initial mode of results disclosure, in this case the letter, appears to be central to minimizing the adverse emotional impact of trait notification. Parents also cited sources of additional information that they sought out following receiving the notification, indicating that effective educational strategies may help minimize the stress experienced by notified parents. Key stakeholders to engage include included healthcare providers, namely the infant's pediatrician, as they were often named as a primary reference for families. Other external sources of information included family, friends, and coworkers. Only one parent spoke of turning to the internet ("Googling") for more information.

Personal and familial experience with SCT appeared to both positively and negatively influence emotional reaction to the trait notification depending on the nature of the experience. Many of those who denied having a negative reaction to the letter explained that they had family members with SCT who were generally healthy. In the case that the experience was negative, this was often noted in tandem with a self-report of anxiety. Specifically, a number of participants who reported being made anxious by the letter spoke of having family members affected with SCD. One mother talked about her father who had SCT that "developed into a rare form of SCD," evoking confusion between SCD and SCT.

These observations are generally consistent with community-based qualitative studies that have found familial connections to be central sources of health information in African American

communities.[16,122–124] They also suggest that education of PCPs and other healthcare providers, as well as community outreach may go farther than paper or web-based educational material in promoting SCT awareness and understanding among high-risk populations. Community-based educational programs have been shown to be effective at promoting SCT awareness and screening in at-risk populations.[15,120]

As was true for the first part of survey, the results of this section may also inform Kladny et al.'s assessment of the ability of follow-up services to reduce anxiety in parents who have been notified of positive NBS SCT results through the mail. In this previous study, families were asked if they "felt less anxious after watching the video" that was provided to them following trait notification.[24] Ninety-two percent of families reported that the video decreased their anxiety. In a follow-up study by Kladny et al., families who received in-person genetic counseling for SCT were asked if they felt less anxious after the session.[22] In this case, 82% of families indicated they felt less anxious. However, in neither survey were parents asked if they were anxious before the video or genetic counseling. Findings from this current study indicate that a substantial proportion of parents do experience lingering anxiety due to trait notification and may benefit from these follow-up services to promote emotional wellbeing.

Taken together, these studies' findings provide insight into the criticism that more aggressive follow-up for SCT may unnecessarily increase anxiety.[49,157] The previous work performed by Kladny et al. demonstrates that additional services following trait notification by mail reduces anxiety in notified mothers; this study identified a proportion of parents who may benefit from access to such services. With thoughtful execution, follow-up for SCT notification may minimize the potential emotional harm caused by the NBS program. A prioritization should also be placed on making the initial notification clear and reassuring and providing mothers with

immediately accessible sources of accurate information. One source that the current letter provides is the number to the Pediatric Hemoglobinopathy RN Coordinator. Future assessment must be done to determine to what degree this number is utilized and its effectiveness at minimizing initial anxiety in notified families. A survey of PCP knowledge in regarding SCT may also help to design training and resources for

3.4.3 Aim 3: Sharing Patterns

Evidence for stigma related to SCD in African American communities has raised concern that parents may not feel comfortable sharing the screening results. This is supported by lower rates of SCT status awareness than universal newborn and targeted prenatal screening programs would suggest (Table 5).[17,119] While individual circumstances vary, discussion of the health information with close family members and healthcare providers promotes more full realization of the reproductive benefit of SCT notification. The great majority of parents surveyed in this study reported their intent to discuss the NBS results with relevant individuals. This high rate of anticipated sharing is consistent with the findings of past studies of similar populations.[17,18,22,24]

The NBS program's potential to provide reproductive benefit to the screened newborn relies on the health information being shared with him or her at an older age. When parents in this study were asked whether they planned to share the letter's information with their infant at a later date, all but one individual confirmed that they did. A substantial proportion of telephone survey participants replied emphatically to this question, underlining their intent to share the health information. While the age at which they planned to share this information was not asked for, the majority of participants who elaborated on the question mentioned the milestones of dating and

reproductive age as pertinent to the time of disclosure. This indicates an appreciation for the information's implications.

This study's measured rate of reported sharing with the infant exceeds that of Kladny et al., in which 91% of mothers who had received genetic counseling for SCT confirmed that they planned to tell their infant about the NBS result at an older age.[22] This suggests that trait notification through a letter alone may be sufficient in promoting sharing with the newborn who receives the screening through NBS. However, future studies are needed to determine if such discussions actually do occur and how their quality may be impacted by the way families are presented with the information.

The great majority of parents in this study (96.8%) reported that they felt comfortable discussing their child's trait status with their partner. Several telephone survey responses indicated that these conversations may be limited. One mother qualified her response by saying that while she would discuss SCT, she "wouldn't want to discuss disease." Another replied that while she was comfortable, her partner would "clam up." Three other parents who reported feeling comfortable discussing SCT similarly indicated that when they tried to bring up the topic, their partner had not been receptive. However, this was the minority of parents. Many more indicated they were able to discuss SCT comfortably with their partner.

This rate of reported sharing with one's partner is similar to that found by Lang et al. among notified mothers living in Illinois.[17] Similar to this current study, Lang et al. called mothers eight to 52 weeks after their infant's birth to administer a survey regarding awareness and knowledge of SCD as well as anticipated sharing patterns. Ninety-seven of the 100 participants (97%) confirmed that their partner should also be made aware of their infant's positive screen for SCT. The survey provided additional insight into potential barriers to sharing the information, as participants were

presented with three answer choices to the question of whether their partner knew that their child had SCT: 1) Yes, they should know, 2) No, it does not matter if they know, and 3) No, I do not want them to know. The three mothers who did not respond that their partner should know their infant's positive SCT screen identified that it was because it did not matter whether or not their partner knew. No participant replied that she did not want her partner to know. Thus, the mothers surveyed by Lang et al. appeared to desire to share this information with their partner if they believed it was important. Appreciation for the pertinence of their infant's positive SCT status may serve as a more significant barrier to sharing the information of an infant's positive screen, rather than a desire to not share it.

Genetic counseling, which was shown by Kladny et al. to provide relevant knowledge and reduce anxiety, also appears to affect parents' rates of sharing with family members. When Kladny et al. surveyed notified mothers following a genetic counseling session for SCT, significantly more mothers said they planned to discuss SCT with their partner than those who confirmed that they had discussed SCT with their partner before or during pregnancy: 81% versus 21%.[22] Kladny et al. interpreted this rise in sharing rates following genetic counseling to demonstrate that genetic counseling *promotes* sharing of the health information between partners. However, this increase may have been influenced by other factors, including notably, a lack of awareness that SCT was a possibility for the pregnancy. It may also indicate a difference in the self-reported measure as it concerns past sharing versus anticipated sharing, as participants may be unrealistically optimistic about their future actions. Lastly, an inability to confirm whether or not these discussions about SCD actually do occur, as well as their relative quality, is a significant limitation of both this and the previous studies.

At 91% and 81% respectively, parents' reported rates of sharing with one's infant and one's partner were lower in the studies of Kladny et al. than those reported by parents in both this current study as well as that of Long et al.[17,22] Genetic counseling itself may reduce sharing rates with these relevant individuals. This could be the case if lower anxiety was related to lower sharing rates, or if the education provided during genetic counseling informed parents that further discussion of the results with these family members was not necessary. Such a finding would be an important topic of future research, as lowering rates of sharing with these two individuals is generally counter to the goals of a genetic counseling session. A number of other explanations exist that are unrelated to the intervention of genetic counseling, however. First, none of these studies clarified if the reproductive partner specified by the survey was the other parent of the baby or one's current partner, if these two individuals differed. In the case that they did, varied interpretations of parents may have contributed to discordant rates of sharing between the studies. Additionally, although it is not clear how it would contribute to lower sharing rates, self-selection bias was more heavily implicated in the population of Kladny et al., as participants were required to pursue additional follow-up counseling services.

In this current study, higher rates of sharing were reported with both specified family members than with the healthcare providers who were named. Sharing rates may indicate parents' views on the importance of the information for the named individuals; in the case of healthcare providers, lower rates of sharing may also reflect a communication gap between medical providers and the African American community, which has been well-documented.[101,138,162] However, the great majority of parents still reported an intent to share the letter's information with both their infant's doctor, as well as their own. When participants were asked if they intended to share their infant's SCT status with their PCP, over 90% confirmed that they already had or intended to tell

them. In many of the telephone responses, parents expressed that it was their infant's PCP with whom they had initially discussed the NBS results. The infant's PCP would have also received the NBS results if they were listed on the NBS blood spot, and parents were not asked whether they or the physician had initiated the reported conversation.

A number of participants surveyed over the telephone expressed that their PCP should already know the screening results. This suggests that a decision to not share this information may derive from a belief that they are already aware of the results, rather than discomfort over discussing the results or a preference for them to not know their infant's trait status. However, this assumption of parents that their infant's PCP is aware of the screening results may not be true under a number of circumstances. First, while the PCP listed on the NBS bloodspot is notified of the results in Pennsylvania's NBS program, this provider may not accurately reflect the infant's actual PCP. In the case that it does not, the infant's PCP would not receive the results through NBS. Additionally, a 2007 survey of NBS programs for SCD found that unlike Pennsylvania, 12% of states had NBS programs that did not directly notify the infant's PCP of a positive screening result for SCT.[21] This same study also found that among those programs that did include notification of the PCP for SCT results, less than half possessed a confirmation mechanism, such as a return fax, electronic log, or telephone log, to ensure that the specified provider actually received the results notification.[21]

The lowest rate of anticipated sharing (71.3%) was found regarding the parent's own physician. This individual was the only specified stakeholder with whom less than 90% of participants reported an intent to discuss the screening results. Lower rates of anticipated sharing may reflect a lack of clarity among parents regarding the screening result's relevancy to their own potential for having a pregnancy affected with SCD. This interpretation is consistent with the

results from the knowledge assessment, which showed a lack of clarity about the specific inheritance pattern of SCD. However, a number of parents who reported no intention to discuss their infant's screening results with their own physician responded that their infant's positive SCT status "came from their partner." While this does demonstrate an understanding of the letter's implications for the parents' carrier status, the interviewers did not seek to clarify whether this was an assumption or had been confirmed by hemoglobinopathy screening. Moreover, if a respondent's partner does have SCT, it is more relevant that the they determine their personal SCT status, which may be facilitated through speaking with their physician.[20] As previous studies have shown a generally low perception of personal risk for having a child with SCD, along with sub-optimal uptake of hemoglobinopathy screening, further evaluation of the SCT notification process calls for looking at its effect on promoting hemoglobinopathy screening in parents of undetermined SCT status.[15–18,130,131]

3.4.4 Study Limitations

This study sought to evaluate the impact of the NBS program on families in Western Pennsylvania who had been notified of their infant's positive result for Sickle S or HbC trait within the past year. However, its ability to draw conclusions regarding the overall effect of the program are limited by its exclusion of a meaningful subset of families and family members.

First, while effective trait notification requires the letter to be received and read, parents who reported that they did not recall receiving the notification were ineligible for this study, which sought to describe the specific effects of the letter. The perspectives of these individuals are pertinent to a comprehensive evaluation of the trait notification program, and as a consequence of their exclusion, this study does not fully describe the program's impact. Both its positive and

negative effects are likely more acutely felt by those who do receive the notification letter. Thus, it likely inflates the program's impact, both in terms of its harms and benefits.

This study also largely fails to describe the experiences of fathers with the NBS trait notification process. While both fathers and mothers were eligible to participate in the study, the great majority of survey participants were mothers. Only two of the 81 telephone surveys were completed by fathers. The mail survey did not ask whether it was the mother or father who was responding which precludes quantification of how many fathers did participate in the study. However, the survey was addressed to the mother, as this is whose contact information is reported on the NBS bloodspot. Consequently, it is assumed that the great majority of mail respondents were also mothers. A lack of male representation is a common criticism of the current literature regarding sickle cell health beliefs and behavior; this study is similarly limited in its generalizability to the experiences of *parents* with the NBS trait notification program and represents primarily mothers.

As another point to consider, sampling bias may have inflated this study's conclusions regarding the NBS program's impact. This would be the case if those who agreed to participate differed from the general population of notified parents in ways that differentially impacted measurements. Survey responses were obtained for approximately 22% of parents who should have received the notification letter within the past year. When surveyed over the telephone, 81 of the 140 eligible participants who were contacted consented to participate. Through the mail, 13 completed surveys were obtained out of the 394 surveys that were not returned as undeliverable. This translates to response rates of 57.8% through the telephone and 3.3% through the mail. These rates reflect the magnitude by which sampling bias may impacted the study's results. Regarding its potential effect on knowledge measurements, it is plausible that those who felt more uncertainty

regarding the questions did not complete or send back the mail survey. Similarly, those contacted by telephone who felt uncertain about their understanding of SCD may have declined to participate, as the consent process explained they would be asked a series of true/false and multiple-choice questions about SCD.

The survey sought to measure emotional impact and to gather feedback about the letter. This may have implications for sampling bias as well. During the consent process, participants were informed that it was a goal of the study to utilize the information it gained to revise the letter, so that the notification process could potentially be improved. Parents for whom the letter elicited a strong emotional reaction, or who found its information to be especially important, may have been more likely to remember the notification and/or to be inclined to participate. Consequently, it is plausible that this survey found a magnified impact in its latter two sections (Anxiety and Sharing) due to sampling bias.

A strength of this study is the utilization of both mail and telephone surveys, which allows for an examination of the potential effect of reporting bias through comparing the two methods' results. Reporting bias arises in self-reported measures when participants purposefully give false information due to their reluctance to report the truth, as it may be perceived as socially unacceptable or undesirable.[163] Previous studies have sought to assess the impact of different survey modes on measurements of health-related quality of life, emotional, and behavioral data. These studies have generally found a small yet significant impact in the survey mode. When surveyed over the telephone as compared to mail, participants tend to report more positively about their mental health and emotions and are less likely to report socially-unacceptable behavior.[163–166] This pattern, which can be attributed to the greater anonymity of the mail format, has implications for this study. For example, parents may have been more likely to understate a

negative reaction to receiving the letter or to falsely report their intent to share the letter's information with particular individuals. The error in measurements of this data would be expected to be greater for the telephone surveys than for the mail surveys based on findings from these previous studies.

Nearly identical rates of emotional distress were found for part two (Anxiety). However, the different survey tools (PROMIS survey versus a single question) are likely more relevant than survey format and preclude this comparison between mail and telephone survey measurements. For the final section of the survey (Sharing), reporting bias would be expected to lead to artificially high rates of anticipated disclosure of the SCT results. Again, the influence would likely be greater in the case of the telephone surveys, where there was more direct contact between the subject and the interviewer. Attempts were made to minimize this bias by reminding participants that there was no right or wrong answer, yet a number of participants responded to the question by asking if they "should share the information" with the specified individual. For all individuals whom this section addressed (the participant's infant, partner, PCP, and infant's PCP), the reported rates of sharing were equal or higher when measured by the mail, as compared to the telephone (Appendix H.2). As this is the opposite pattern as would be expected with reporting bias, this bias likely had minimal impact in this third section of the survey (Sharing). More direct measurement is needed to ascertain whether this *intent* to share the trait notification letter's information does translate to it being effectively imparted to important stakeholders.

3.4.5 Future Research

Disclosure of SCT status is not a primary goal of NBS, as the carrier state does not jeopardize the health of the infant.[1,82,111] While it may be argued that promoting parents'

reproductive choice is a potential benefit of the program, states' decisions to disclose the incidental finding are based on a position that the health information belongs to the infant. The screening results are shared with their parents only in their capacity as the infant's guardians.[8] As this study did not examine the program's effect on the newborn, it calls for this as a follow-up study to more fully describe the program's appropriateness.

Data collected through this study will be used to suggest revisions of the current SCT notification letter sent to parents in Region 6 of Pennsylvania. A repeat assessment of parents who receive the updated mailed information would permit an assessment of how the letter's modifications have impacted parents' knowledge, anxiety and disclosure patterns through a comparison with this study's data. A number of additional measurements, described below, could also be collected at this time to augment the evaluation of trait notification through NBS that this current study provides.

In their evaluation of a systematic follow-up process for SCT results disclosed through the mail, Kladny et al. noted that it could not be determined how many of the NBS letters are actually delivered to the correct individual, as well as opened and read.[192–194] Receiving and reading the letter comprise the minimum set of actions required for the trait notification letter to have an effect on parents. An inability to ensure that this occurs is one major criticism of the passive means of trait notification provided by a letter. Through administering the telephone survey, it was found that 2.9% of parents who were reached reported not receiving the notification letter. It is reasonable to posit that parents who could not be reached for the telephone survey, either because the number was disconnected (23.3% of all attempted calls) or incorrect (5.7% of calls), are also those individuals more likely to have not received the notification letter. As this was the only means this study had to assess whether parents had received the original trait letter, this study cannot provide

an accurate estimate of the rate that the notification letter is received, opened, and then read by families. Further evaluation is needed to more determine this. Without such data, the effectiveness of the NBS program cannot be fully appreciated.

The second part of this survey aimed to gauge anxiety as a potential psychological harm of trait notification. There are a number of other ways this program may negatively impact the emotional and social wellbeing of its targeted population. These include relational distress between notified parents due to the future reproductive implications of the information or questioned paternity, feelings of guilt or blame, and impaired self-image of those found to have with SCT.[10–13,49] Additional research should explore these risks of trait notification as they relate to the current method of a letter in order to better understand the specific program's impact.

Finally, as it was deemed a deficit of the studies of Kladny et al, this study also lacked a baseline for its measurements. Consequently, this study cannot clarify whether the trait letter alone has any effect on SCD knowledge. A number of similar assessments of SCD knowledge, which were reviewed earlier in this text, may provide comparisons (Table 5). However, their scores demonstrate a great sensitivity to population demographics, specific questionnaire, and survey technique. Ideally, pre- and post-notification knowledge surveys would be administered to measure any direct effect of the notification process. While this cannot be feasibly performed in parents who have not yet been notified of their infant's positive screen, an opportunity for this does exists in a NBS program that does not currently directly notify families of SCT results. Assessing SCD knowledge in communities where prevalence of SCT is highest, prior to and then after initiation of a trial program, would provide valuable insight into the actual effect such a program has on a community's awareness and understanding of SCD. One component of public health services such as NBS is assessment and quality improvement. Such a trial may fill this role.

3.5 CONCLUSION

This study sought to evaluate the impact of SCT notification on the families whose infants had been identified through Western Pennsylvania's NBS program to have a variant hemoglobin trait. Its findings suggest that the current notification process does not fully convey to parents how this positive hemoglobin trait status impacts health and reproductive risk. Comparison of this study's findings to those of previous work, which also surveyed notified parents living in Western Pennsylvania, indicates that follow-up educational and counseling services may help to maximize the educational benefits of the NBS program for SCT. These services may also reduce the anxiety associated trait notification, with emotional distress being reported by approximately one third of this study's participants. Finally, the great majority of parents surveyed by this study stated their intent to discuss their infant's positive SCT status with relevant family members and healthcare providers. This suggests that the notification letter's health information is generally found to be useful by families and that they appreciate its relevance. Notified parents may benefit from additional encouragement to discuss the screening results with their own physician in order to promote informed reproductive decision making.

While previous literature has explored the three parameters addressed by this study – SCD-related knowledge, anxiety regarding carrier status, and openness towards discussing SCT with family and healthcare providers – less work has looked specifically at how they may be influenced the disclosure of SCT status through NBS specifically. This means of information transmission is important to address, as greater awareness of SCD and personal trait status is supported by both the lay and medical communities it most concerns; it is the setting of NBS that is primarily contended. There is currently no consensus on the appropriateness of sharing newborns' SCT status when incidentally identified through NBS, yet variant hemoglobinopathy traits are the most

common screening result in the Pennsylvania NBS program.[106] This study's value lays in part in the gap between the high frequency of this NBS result and the little agreement between states' programs in how to handle it.

This work may contribute to forming a consensus regarding sharing of hemoglobin variant trait status through NBS. It increases understanding of one NBS program for SCT notification, both as the majority of families experience it, as well as how it may be more ideally carried out. In relation to the latter, it augments previous work performed in the same population of notified parents in Western Pennsylvania, which examined the impact of genetic counseling services following trait notification through the mail.[22,24] A comparison of these studies' results suggests that follow-up services may both increase the trait notification's informative benefits and reduce its potential for emotional harm.

Follow-up educational and counseling services are often unavailable or underutilized by families of infants who screen positive for SCT, however.[21,73,120] As a consequence, the passive means of trait notification that this current study examined likely represents a more common experience for notified families. Comparison of this study's results to those previously obtained by surveying mothers who had been notified of their infant's positive SCT results through a mailing sent by the Illinois NBS program further clarifies the common strengths and weaknesses of trait notification through a mailing.[17] As one key finding, ensuring that parents understand the minimal health effects of SCT and the specific inheritance pattern of SCD appears to be a significant limitation of trait notification through the mail in general.

Together, these studies advocate for NBS resources to be devoted to additional educational and counseling services for notified families. As limited resources provide a barrier for expanding this public health service, further work must be carried out to identify services that are both

effective and may be feasibly implemented. Such evaluation should include clarifying what specific information should be prioritized to maximize the reproductive benefit of the NBS program, for both the parents as well as for the screened infant. Finally, as did this study, future work must directly engage with the communities most affected by the NBS program as key stakeholders in the NBS trait notification process.

4.0 RESEARCH SIGNIFICANCE TO PUBLIC HEALTH AND GENETIC COUNSELING

Evaluation of current services for quality improvement is a central component of the NBS program.[167,168] This study, which examined the impact of SCT notification on families living in Western Pennsylvania, was carried out in part to serve this quality improvement role. Through examining the NBS program for SCT notification, this study also fulfills the core public health function of assurance, which aims to ensure the accessibility and effectiveness of public health interventions.[169] There are a number of other ways that this work may provide assurance in the public health program as well. Through gathering data to guide revision of the current SCT letter sent in Western Pennsylvania NBS, this survey of parents provided insight that may be used to improve the trait notification process. Measurements obtained through the survey may also provide a baseline for evaluation of the revised letter and potentially inform the assessments of other states' programs. With the goal of being relevant to such future assessment roles, this study was guided by models of public health program evaluation that propose weighing the potential risks with the benefits.[111,115]

Questions regarding the appropriateness of carrier identification in newborns extend beyond sickle cell. SCT is not the only carrier status discovered incidentally through current NBS programs. Heterozygous carriers of the congenital lung disease cystic fibrosis (CF), which is also included on the RUSP, may be identified through NBS.[9] With a carrier rate of one in 25 among individuals of Western European descent, CF has been the focus of similar assessments of carrier status disclosure through NBS.[140,170] In the case of CF, the incidental carrier status is typically identified through follow-up diagnostic testing following a positive NBS result.[158] While key

differences in carrier notification exist between these two conditions – namely the circumstances of carrier identification, the degree of provider involvement, and the different populations most greatly affected – similar concerns have been raised regarding inadequate education about the health and reproductive implications of the carrier state, as well as undue parental anxiety.[140,158,171] Thus, this study's findings may have broader applicability, extending to carrier status notification through NBS more generally. A greater understanding of the effects of such NBS programs is becoming increasingly salient, as states' panels are being further pushed to expand.[82]

With the potential growing for more carrier infants to be identified incidentally through NBS, advocates for an increased scope of the public health program suggest that reproductive benefit may be designated as one of its primary purposes.[117,172] A number of professional groups challenge this view, yet they do concede that disclosure of carrier screening results through NBS may offer secondary benefits to the infant's parents.[125,173,174] A statement from ASHG calls for "additional research to assess the utility of disclosing carrier results generated from NBS for reproductive decision-making and cascade testing."[125] This study adds to that body of knowledge called for by ASHG. It contends that programs must be robustly supported by educational resources, both for families as well as physicians, for carrier identification to more fully realize its potential. Through minimizing confusion about the genetic information, parental stress related to the notification may be reduced and the information better utilized. Further education may also inform the discussions that this survey's parents reported they intend to have with at-risk family members. These conversations are necessary for both the informed reproductive decision-making and cascade testing specified by the ASHG statement.[125]

As it was informed by previous studies of Kladny et al., this study also further clarifies how genetic counselors may support SCT notification programs in better attaining their goals.[22,24]

As noted by one SCD patient advocate, a key barrier to increasing sickle cell awareness and informing reproductive choice is the "racial and cultural differences between the patient and members of the healthcare community…that impede effective communication and therapeutic relationships."[162] With the genetic counseling field's particular emphasis on acknowledging clients' social and familial dynamics, culture, and religion, genetic counselors may be particularly adept at overcoming these racial and cultural barriers, thereby facilitating the informed choice and adaption to risk that drives SCT notification.[175] However, the historical involvement of genetic counseling in sickle cell screening is complex and has not always been positively regarded: It is important that the profession look to this past as a tool to improve its interaction with affected communities, rather than as discouragement toward future involvement. Through direct engagement with the parents and communities affected by SCD, genetic counselors' services may be better directed to the communities' needs and desires. Genetic counselors must also continue their efforts to increase the racial and cultural diversity of their own profession.

The importance of this conclusion further rests in evidence that genetic counseling services are inaccessible to many parents following trait notification and when offered, are underutilized.[21,22,24,73] This study's findings call for genetic counselors to assess barriers and identify mechanisms that may increase access and utilization of their services following trait notification. Alternative service modes, such as group counseling or telephone counseling, have previously been demonstrated to have success in the sickle cell community.[15,24,120] Their wider implementation could increase the reach of genetic counselors, as they work to serve the essential public health service of informing and educating individuals about their own health.[169]

Genetic counselors may also work to inform other healthcare providers in the discussions they have with families about the SCT results. While the educational role of genetic counselors is

often directed at patients, it may also extend to healthcare professionals. In particular, this study identified PCPs o be key resources for notified parents following the SCT notification. However, PCPs report feeling underprepared to discuss positive NBS results with families.[149,150,153,160] Genetic counselors' help in the development of educational programs to promote skills in supportive communication and explaining the genetics of sickle cell in particular provides a secondary means to employ their specialized training to positively impact the trait notification process for families. Through this role, genetic counselors may better assure proficiency of the workforce, which is another essential public health service.[169] Arming these providers to counsel about the SCT screening results as well as about NBS more generally would significantly increase the healthcare provider workforce who is available to assist families made anxious and confused by learning of their infant's positive SCT screen through the NBS letter.

Finally, partnering with community-based organizations has been shown to be effective in increasing knowledge and promoting awareness of personal trait status among at-risk populations.[15,131] In Pittsburgh, where this study was conducted, the Children's Sickle Cell Foundations (CSCF) is one organization that exists to support families affected with SCD. Working with CSCF and other community-based partners, such as public schools, can help bolster the resources that are available for families who receive the SCT notification. This study calls for the mobilization of such community partnerships, so that the benefits of NBS programs may be more fully experienced by the notified families of Western Pennsylvania.[169]

5.0 PUBLIC HEALTH ESSAY:
EVALUATION OF A QUALITY INITIATIVE TO IMPROVE PENICILLIN PRESCRIPTION IN PEDIATRIC SICKLE CELL CLINIC

5.1 BACKGROUND

Sickle cell disease (SCD) encompasses a family of inherited blood disorders characterized by structurally variant forms of hemoglobin.[3,4] It is a chronic condition estimated to affect between 72,000 to 100,000 individuals in the United States.[30] Approximately 300,000 babies are born with SCD each year throughout the world.[26] In 2006, the World Health Organization (WHO) declared SCD to be one of its top global health priorities.[26] SCD continues to be a significant public health concern in the United States, as well as throughout the world.

5.1.1 Molecular Genetics of Sickle Cell Disease

SCD is a genetic condition caused by biallelic pathogenic variants in the hemoglobin beta gene (*HBB*), which results in the production of abnormal forms of hemoglobin. All individuals with SCD have at least one copy of the HbS allele.[3] In the HbS allele, an adenine to guanine point mutation in the sixth codon of *HBB* results in the substitution of glutamic acid for valine (Glu6Val).[29,69] This gives rise to Hemoglobin S, or Sickle Hemoglobin. Individuals with SCD may have a second copy of the HbS allele or another variant allele that affects *HBB* gene expression or protein structure.[3] The HbC allele (Glu6Lys) is the second most common structural *HBB* variant that leads to SCD.[31] It also arises due to a point mutation in the sixth codon of *HBB*, which in this

case results in substitution of a lysine residue in place of glutamic acid. Mutations in *HBB* that affect gene expression, rather than protein structure, are denoted as thalassemia alleles. β^0 Thalassemia corresponds to no *HBB* gene expression, while β^+ Thalassemia refers to a mutation that results in reduced *HBB* gene expression.[31]

Hemoglobin is the chief oxygen transporter in the blood and is found at particularly high concentrations in the red blood cells (RBC).[28] The HbS allele results in the production of Hemoglobin S (HbS), or Sickle Hemoglobin. HbS is less soluble than normal adult hemoglobin (HbA) and polymerizes under low oxygen concentrations. Chains of polymerized HbS distort the RBCs.[35] The consequences of this deformation on both the RBCs themselves and the surrounding vasculature account for the majority of SCD pathophysiology.[4] Repeat sickling damages the cytoskeleton of the RBCs, so that these cells are removed prematurely from circulation. This shortened lifespan results in chronic hemolytic anemia, jaundice, aplastic crises, and delays in growth as well as sexual development.[3,4] Additionally, sickled RBCs form aggregates that block blood flow in the microvasculature. This is known as vaso-occlusion and leads to episodes of extreme pain, extensive tissue damage, and eventual tissue death due to lack of blood flow. The diverse consequences of chronic hemolytic anemia and vaso-occlusion events give rise to the multi-systemic involvement of SCD.[3,4]

Clinical manifestations of SCD are not present at birth. Rather, symptoms arise during infancy, once pathological concentrations of HbS are reached in the RBCs.[28] Prior to this time, the fetal form of hemoglobin, HbF, predominates, providing a protective effect. At sufficiently high cellular concentrations, HbF precludes RBC sickling. It cannot itself polymerize and thus, interrupts the polymerization reaction of HbS at high enough concentrations.[27] Developmentally regulated differential gene expression at the beta-globin locus is responsible for the gradual

increase in *HBB* expression in relation to *HBF*, which is necessary for the synthesis of HbF.[28] The gradual switch from fetal to adult hemoglobin expression begins before birth, with HbA predominating over HbF in the blood by around six months after birth. This timing correlates clinically to the period in which the significant risk for mortality emerges in SCD, between six to twelve months of age.[3,176]

5.1.2 Infection in Sickle Cell Disease

Infection is one of the earliest life-threatening complications of SCD.[4] Between three and six months of age, infants with SCD develop an increased susceptibility to sepsis and meningitis due to infection from invasive bacterial species.[177] Without intervention, the risk for infection in SCD is estimated to be between 30 to 600 times higher than that of an age and race-matched population.[178] Susceptibility decreases with age, so that the greatest risk presents before age five.[4,179] In the United States, approximately 30% of affected children under the age of five years old died from infection prior to the introduction of effective treatment methods.[179–181]

Several early studies helped to clarify this high risk of infant mortality in SCD and attribute it to pneumococcal infection. In a retrospective case review of autopsies completed in Memphis, Tennessee in the early 1970s, the director of the first comprehensive sickle cell research center, Lemuel Diggs, estimated that one-fifth of deaths among those with SCD occurred prior to age 2.[182] One quarter of all deaths occurred prior to age five. In both groups, the primary cause was infection. Another early retrospective cohort study of 276 children with SCD born in Jamaica between 1952 and 1982 had similar findings. Among these individuals, the highest risk for death occurred before age five, and more specifically, between six and twelve months of age. In these children as well, infection was the most common cause of death.[42]

Infant mortality was the focus of one of the inaugural projects of the Cooperative Study of Sickle Cell Disease (CSSCD). The CSSCD was conceived to be the largest epidemiological study of SCD to date with an aim of clarifying the condition's natural history.[78] Through funding provided by the Sickle Cell Anemia Control Act, the National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health (NIH) sponsored this multi-center study beginning in 1978.[2] Through the CSSCD, more than 600 newborns with SCD were identified through screening performed at birth.[183] Upon diagnosis, newborns were enrolled for ongoing clinic follow-up for their first two years of life. Data that were collected over the course of this study demonstrated a strikingly high frequency of acute events of bacterial meningitis and sepsis in infants with SCD.[183] A follow-up study through the CSSCD was published six years later in 1995 and once again found infection to be the primary cause of death in its affected population under the age of five years old.[176]

5.1.3 Immune Dysfunction

Vulnerability to infection in infants with SCD is due to immune dysfunction primarily relating to the spleen.[179,184] As the largest organ of the lymphatic system, the spleen plays a multifunctional role in maintaining the body's immunity.[185]

The spleen serves as a mechanical filter for the circulatory system. Old and damaged RBCs, as well as bloodborne pathogens, are removed as blood flows through its endothelial slits.[178,184] Macrophages metabolize the waste, aiding in the prevention of infection by circulating microorganisms.[185] Additionally, the spleen is integral to the humoral and cell-mediated pathways of the adaptive immune system. It is the site of maturation for memory B-cells, which are the body's main defense against encapsulated microorganisms.[185,186] Memory B-cells are needed for

opsonization, a process exclusive to the spleen in which encapsulated bacteria are removed by macrophages via phagocytosis.[186] Individuals with reduced splenic function, such as those with SCD, exhibit a deficiency in memory B cells.[187] This contributes to an impaired clearance of bacteria and consequently, an increased susceptibility to infection by invasive pneumococcal species.

Functional Asplenia: While the spleen is functionally and morphologically unaffected at birth, it is one of first organs impacted during the progression of SCD.[4,184] Signs of damage can be observed as early as three to four months of age in those with HbSS disease.[188,189] The pathological course that leads to insufficient splenic function is complex, but is believed to arise secondary to vaso-occlusion.[184] The deoxygenating conditions of the spleen are a particularly potent stimulus for the sickling of RBC.[184] Because sickled RBCs are more rigid than round RBCs, they are prone to becoming entrapped in the organ's microvasculature.[187,190] Congestion of the splenic filtration system by sickled RBCs can lead to pooling of blood and acute or chronic enlargement of the spleen. The latter, known as splenomegaly, is one of the most common complications of SCD.[4] Congestion of the splenic filtration system can further compromise the spleen's ability to remove bacteria from circulation. This leads to an increased risk of invasive pneumococcal disease (IPD).[191]

Complete loss of splenic function is known as functional asplenia and is a common development in the natural history of SCD.[189,192] Also termed autosplenectomy, it is a consequence of repeat vaso-occlusion events, which cause splenic tissue ischemia, infarction, and eventually fibrosis. Over time, the spleen atrophies and is rendered non-functional.[184] Among those with HbSS disease, functional asplenia is typically exhibited between six months and five years of age.[4,192] In one study performed through the CSSCD, approximately 14% of infants with HbSS

disease demonstrated partial or fully compromised splenic function by six months old; by age five, the prevalence had increased to nearly 94%.[40]

Surgical Splenectomy: Surgical removal of the spleen may be considered in SCD under certain circumstances. Such events include hypersplenia, recurrent or life-threating splenic sequestration, and splenic absess.[19,193] Hypersplenism is defined as splenomegaly in the presence of hematological complications, such as anemia, thrombocytopenia, or neutropenia.[194] One large cohort study found hypersplenism to be present in approximately 5% of its pediatric population with SCD.[195] However, prevalence of hypersplenism in SCD may be higher and is hard to accurately ascertain due to the difficulty in identifying the condition against the background of other common complications of the disease.[184] In hypersplenism, the spleen prematurely destroys blood cells. Compensatory bone marrow hyperplasia arises in response to blood count deficiencies, which can worsen the growth deficiencies commonly experienced in SCD.[184,194] Treatment of hypersplenism may involve chronic blood transfusions, partial splenectomy, or more typically, complete surgical splenectomy.

A more common indication for surgical splenectomy is recurrent acute splenic sequestration crisis (ASSC). ASSC occurs when a sudden enlargement of the spleen leads to a drop in circulating hemoglobin concentration and blood volume. The complication follows infection as the second primary cause of death in infants and children with SCD.[196] For those with HbSS disease, lifetime risk of ASSC is estimated to be between 7% and 30%; the risk is highest in infancy.[39,188,193] In a retrospective case review of 437 ASSC events in children with HbSS and HbS-β^0 Thalassemia, Brousse et al. found that approximately three-quarters of ASSC events occurred prior to age two.[39] ASSC appears to become rare after six years of age.[188] In ASSC, blockage of the splenic vasculature by sickled RBCs results in substantial pooling of blood in the

spleen. Blood volume throughout the remainder of the body rapidly drops, which can lead to fatal hypovolemic shock unless promptly treated with a blood transfusion.[195] Repeat events have been found to occur in approximately 50-70% of individuals.[39,188] Splenectomy may be considered after two occurrences of ASSC in individuals over the age of two years old.[19]

The benefits of surgical splenectomy must be weighed against the potential risks. Namely, surgical removal of the spleen may be associated with a susceptibility to pneumococcal infection that exceeds the already increased risk found in those with SCD. In particular, surgical splenectomy is associated with Overwhelming Post-Splenectomy Infection (OPSI).[197] OPSI is a sudden onset of sepsis or meningitis caused by encapsulated bacteria; death may occur as soon as 24 to 48 hours after the onset of symptoms. Mortality rates are estimated to be between 50% to 70%.[198] However, these rates are derived from older studies that likely do not reflect advancements in care. More recent estimates from retrospective case reviews of OPSI events in England and the United States suggest a mortality rate associated with OPSI that is closer to 10%-30%.[198,199]

Numerous studies have demonstrated an increased risk of infection and death due to OPSI following splenectomy.[211,218] In one retrospective review of 413 children who had undergone splenic trauma, splenectomized children were shown to have a significantly increased risk for overwhelming sepsis, with a 50% mortality rate in the ten events of sepsis that were reviewed.[200] However, this study was not specific to individuals with SCD. The significant increased risk found by the study was relative to the general population risk, rather than that of those affected with an immune-compromising condition such as SCD. Another review of post-splenectomy sepsis events retrieved from the literature between 1966 and 1996 did find that sepsis events among patients who had undergone a surgical splenectomy were associated with a significantly increased mortality rate in children with hemoglobinopathies, such as SCD.[201]

Considering that autosplenectomy occurs in 94% of all individuals with HbSS disease by the age of five, it has been questioned whether surgical splenectomy does increase the risk of IPD in children with SCD.[40,192] In a number of studies exclusive to individuals with SCD, the incidence of infection has not been shown to be significantly elevated following surgical splenectomy. A case review performed between 1988 and 1992 of sixteen patients with SCD who had undergone a surgical splenectomy did not show a significant increase in incidence of infection or sepsis following the procedure.[202] Likewise, a retrospective case review of 37 children with HbSS disease who underwent splenectomies between 1993 and 2008 found that the overall rate of sepsis in this group did not differ significantly before and after surgery.[203] Such studies, which examine infection rate in the same individuals pre- and post-splenectomy, have been criticized for the potential influence that age has been found to have on infection rate in SCD. Specifically, the risk for IPD decreases as individuals with SCD grow older. Thus, the measured post-splenectomy risk for infection may be diminished by the protective effect of a patient's increased age.[183] An additional limitation of such studies that examine infection rate exclusively in individuals who have had a splenectomy is that they may insufficiently capture an increased risk for these individuals relative to other individuals with SCD. This would be the case if splenectomy itself is not a predisposing factor to infection, but rather a surrogate marker for some other cause for a greater susceptibility to infection.

Studies have attempted to address these shortcomings by comparing the infection rate among those with SCD who have had surgical splenectomies with age and sex matched controls who did not. Two such studies, which were performed as retrospective case-control studies, reported favorable post-splenectomy outcomes. They found no significant difference in infection

rate between those who received a splenectomy, both pre- and post-surgery, and those who did not.[204,205]

In spite of unclear evidence, current clinical guidelines consider splenectomy to put individuals with SCD at a lifelong increased risk for IPD.[19,206] Specifically, lifelong use of penicillin is recommended for affected individuals following surgical splenectomy to protect against this presumed increased risk of infection.[206]

5.1.4 Management of Infection Risk

In order to address the increased risk for IPD, penicillin prophylaxis and pneumococcal vaccination have become the standard of care for all children with SCD. Early implementation of these measures before two months of age has been enabled through universal newborn screening and has resulted in significantly improved health outcomes for those with SCD.[207]

Penicillin: The Prophylactic Penicillin Study (PROPS) laid the initial groundwork for reducing infection-related infant mortality in SCD through the strong evidence it provided for the utility of penicillin to prevent IPD. PROPS was a multi-center, randomized, double blind, and placebo-controlled study conducted between August 1983 and June 1985 through the CSSCD.[5]Its aim was to assess the efficacy of penicillin for reducing mortality risk owing to IPD. Two hundred fifteen children with HbSS disease, aged three to 36 months, were enrolled into either the penicillin or control groups. Those in the experimental penicillin group (n = 105) received twice daily 125 mg penicillin V potassium, and those in the placebo control group (n = 110) received twice daily 50 mg doses of Vitamin C. In the initial findings, the experimental group exhibited an 84% decrease in IPD, as compared to the control group: Two of the 105 patients in the experimental group experienced a pneumococcal infection, compared to thirteen of the 110 patients in the

placebo group ($p = 0.0025$).[5] Additionally, there were no fatalities among those taking penicillin, while three fatalities occurred in the control group. The strength of these findings in support of penicillin prophylaxis resulted in the study's termination eight months early. The results from the PROPS trial, which were published in 1986, established that penicillin prophylaxis could significantly reduce the risk of infection due to encapsulated bacteria in children with HbSS disease.[73,208] The study's authors recommended that penicillin prophylaxis be initiated by two months of age.

Newborn Screening: This evidence-based intervention for SCD established by the PROPS study provided an impetus for universal screening of infants for SCD. In the United States, this proceeds through newborn screening (NBS). NBS is a national public health program that aims to detect congenital conditions in newborns for which prompt intervention has been demonstrated to improve long-term health outcomes.[1,94]

In 1987, which was the year following publication of the PROPS study, New York became the first state to screen newborns for SCD.[2] Other states began adding hemoglobinopathies to their NBS programs, with New Hampshire becoming the last state to do so in 2006.[2] This was prompted by the inclusion of hemoglobinopathies on the Recommended Uniform Screening Panel (RUSP), which was published that year to guide the composition of state's screening panels.[9] The RUSP recommends screening for four core hemoglobinopathies: HbSS disease, HbSC disease, HbS-β^0 Thalassemia, and HbS-β^+ Thalassemia.[96] Currently all 50 states, as well as the District of Columbia and Puerto Rico, screen for these upon birth.[2] Other variant hemoglobin traits are detected incidentally during the screening process and are designated as secondary conditions by the RUSP.[96] Consequently, all newborns in the United States are screened for variant hemoglobin traits, such as Hemoglobin D and Hemoglobin E, along with the more common HbS and HbC

traits. These variant hemoglobin traits may contribute to SCD if they are in trans with the HbS allele.[3]

Upon a positive screen for a hemoglobinopathy, infants in Pennsylvania are referred to a hematology specialist for diagnostic testing and comprehensive care. For infants with a confirmed diagnosis, the priority is initiation of penicillin. This should begin by two months of age.[5,19] Prior to age three years old, the recommended dose for infants remains the dosage prescribed in the PROPS trial, at 125 mg of penicillin V potassium twice a day. After age three years old, the dosage is doubled to 250 mg twice daily to account for increased body mass.[19]

Pneumococcal Immunization: In the context of penicillin prophylaxis, pneumococcal immunization further reduces the risk IPD in children with SCD. The 23-valent polyvalent polysaccharide S. pneumonia vaccine (PPSV23) was introduced in 1983, and its administration is currently recommended to all those with SCD at the ages of two, five, and ten years old.[209] The vaccine consists of 23 purified capsular polysaccharide antigens and has been shown to cover between 73-90% of pneumococcal strains.[210] When administered in addition to daily penicillin, PPSV23 has been found to result in a 50% reduction of invasive pneumococcal disease in children with SCD.[210] However, epidemiological studies have shown that PPSV23 vaccination and penicillin alone confer insufficient protection from fatal pneumococcal infection.[79,210,211] Many of the polysaccharides used in the vaccine fail to evoke a immune response in children with SCD, especially those younger than two years old.[210] The risk of IPD in children with SCD taking penicillin who have received the PPSV23 vaccination has still been found to be ten-times higher than that of the general population.[211]

In 2000, the seven-valet pneumococcal conjugate vaccine, Prevnar 7 (PCV7), was introduced and recommended for all children under age two.[212] PCV7 addresses the mechanism of

poor immunogenic response exhibited by PPSV23, as it consists of purified polysaccharide conjugated to protein carriers in order to induce a greater immunological response than polysaccharides do alone.[210] Several epidemiological studies demonstrated that a significant reduction in IPD in those with SCD followed the vaccine's introduction.[79] In a retrospective review of 2,026 affected children in Tennessee, the rates of pneumococcal disease were compared before introduction of the vaccine (1995 to 1999) and after (2001 to 2004).[177] In children under age two, a 90.8% reduction in cases was observed in the post-vaccination time period. In children under the age of five years old, the effect was even greater, with a decrease of 93.4%. Additionally, a population-based retrospective analysis of 1,242 hospitalizations for IPD in children with SCD between 1994 and 2007 in Georgia showed that hospitalization rate owing to infection decreased three-fold over the study period.[211] The study's authors attributed this reduction to the additional protection conferred by PCV7.

In February 2010, the Food and Drug Administration approved a thirteen-valent pneumococcal conjugate vaccine, Prevnar 13 (PCV13) to replace PCV7. PCV13 is more comprehensive, covering additional six serotypes (1, 3, 5, 6A, 7F and 19A) to those covered by PCV7 (4, 6B, 9V, 14, 18C, 19F and 23F).[212] Consequently, it provides coverage for strains not covered by PCV7 that have been implicated in a substantial proportion of the IPD cases that have presented following the introduction of PCV7.[212] While few epidemiological studies are yet available to show an additional impact on infection rate afforded by PCV13, immunogenicity studies have indicated that the supplementation of six serotypes does indeed confer additional protection against pneumococcal disease.[212–215] In the United States, the PCV13 vaccine is currently recommended along with PPSV23 for all children with SCD.[212] Administration of

PCV13 is recommended at the age of two months old, with additional doses at four months, six months, and finally between 12 to 15 months old.[216]

Effect of Intervention: Since the introduction of prophylactic measures as enabled by NBS, childhood mortality rates in SCD have significantly reduced.[79] The Dallas Newborn Cohort (DNC) has provided a unique perspective on the efficacy of this intervention, as recruitment for the study began after the inclusion of hemoglobinopathies into the states' NBS program.[217] Consequently, the DNC is one of the largest cohorts to date of individuals diagnosed with SCD (specifically HbSS disease, HbSC disease, HbS-β^+ Thalassemia, and HbS-β^0 Thalassemia) who have been provided with comprehensive care since birth.

A 2010 publication describing mortality events in the DNC, which included 940 study participants at the time, found that bacterial sepsis was no longer the leading acute cause of death, as it had been in the DNC's initial 2004 review.[79] The authors noted this to be a temporal shift in mortality patterns associated with the introduction of PCV7 in 2000. From this year to that of the study's publication in 2008, no deaths had occurred due to *Streptococcus pneumoniae* sepsis in the 940 participants, compared to four events in the 711 individuals who had been followed over the previous 8-year span of 1991 to 1999. This contributed to the marked change in overall death rates seen among those with HbSS disease and HbSβ^0 Thalassemia specifically. In Era 2 (1991-1999) an incidence of 0.72 deaths per 100 patient years was observed in patients under age two. This decreased to 0.32 deaths per 100 patient years in Era 3 (2000-2007). A similar reduction was seen in the death rate of children between two years old and five years old: 0.35 deaths per 100 patient years were observed in Era 2, compared to 0 deaths per 100 patient years observed in Era 3.[79] Finally, the study found that the a greater proportion of participants were living into adulthood, with 93.9% (95% CI: 90.3% to 96.2%) of those with HbSS disease and HbS-β^0 Thalassemia

surviving to age 18, compared to 85.6% (95% CI: 73.4% to 94.8%) of those in the previous study.[79,218]

Age-Related Infection Risk: Evidence from epidemiological studies suggests that risk for IPD in children with SCD significantly diminish after the age of five years old.[178,179] Findings of a follow-up study by the CCSD Prophylactic Penicillin Study Group, referred to as PROPS II, first evaluated this reduction in risk as it pertained to the potential ongoing benefit of penicillin prophylaxis.[219] Following the same study design as its predecessor, PROPS II was a double blind, placebo-controlled trial that specifically aimed to measure the effect of penicillin in children with SCD above the age of five years old. This follow-up study recruited 400 patients with HbSS disease who had been receiving penicillin prophylaxis for at least two years prior to their fifth birthday and who had also received the PPSV23 vaccine. Those who had received a surgical splenectomy or had previously experienced a severe pneumococcal infection were excluded due to their higher risk for infection. An insignificant relative risk of infection was found to exist for those in the placebo group, as compared to those receiving penicillin ($p = 0.5$, 95% CI: 0.1–2.7). Additionally, in both the treatment and control groups, infection rates due to pneumococcal bacteremia or meningitis were significantly less compared to those younger patients in both the treatment and placebo groups of the PROPS I trial. Specifically, rates of 0.33 pneumococcal bacteremia or meningitis episodes per 100 person-years in the penicillin group and 0.67 episodes per 100 person-years in the placebo group were observed in the older patient population that comprised PROPS II, compared to 1.5 episodes per 100 person-years in the penicillin group and 9.8 episodes per 100 person-years in the control group of the PROPS I trial. These findings contributed to the clinical recommendation that penicillin be discontinued after the age of five years old in individuals without other risk-increasing factors.[208]

5.1.5 Current Guidelines

In 2014, an expert panel commissioned by the National Heart, Lung, and Blood Institute (NHLBI) of the US National Institutes of Health (NIH) put forth an updated set of Evidence-Based Management guidelines for SCD.[19] These guidelines were developed based on available scientific evidence and expert consensus and are generally consistent with the American Academy of Pediatrics (AAP).[206]

In its consideration of penicillin prophylaxis, the committee evaluated one observational study and three randomized-control trials, including the original PROPS I trial.[5,219,220] The studies included 951 individuals under the age of five years old, among whom 95% had HbSS disease, 5% had HbSC disease, and 1% had HbS-β^0 Thalassemia. Across these studies, daily penicillin was found to be associated with a significant reduction in risk for IPD. The risk reduction in mortality was not found to be significant; however, the evidence regarding mortality was deemed to be low quality and imprecise due to the small total number of mortality events. As a result of their evaluation, the committee put forth strong recommendations supported by moderate-quality evidence that twice-daily oral penicillin be administered to children with HbSS disease up to age five.[19]

While the guidelines state that there is strong and clear evidence for the provisional discontinuation of penicillin after the age of five, the committee presented weak recommendations with moderate-quality evidence that penicillin should be discontinued in children with HbSS disease after age five years old.[19] The recommendation applies to only those individuals who have not had a splenectomy or IPD. The committee also emphasized the necessity of assuring that the recommended pneumococcal vaccination series had been completed prior to penicillin

discontinuation; in the case that it had not, this should be completed as soon as possible and prior to discontinuing penicillin.

Specific guidelines regarding pneumococcal vaccination were also presented in the NIH document. A strong recommendation with moderate quality evidence was made for the administration of PCV13 and PPSV23 according to the time-courses specified by the Advisory Committee on Immunization Practices of the Centers for Disease Control and Prevention (CDC).[19] Children with SCD were recommended to follow the time course for individuals with immune-compromising conditions published in the "Childhood and Adolescent Immunization Schedule."[209] According to these guidelines, the PCV13 series should begin shortly after birth for infants with SCD. Additionally, the first does of PPSV23 should be administered at age two. The second dose should be given at the age of five, rather seven, as it is more generally advised. This is to provide adequate protection following discontinuation of penicillin at age five.

Guidelines for other SCD Types: In the NHLBI management guidelines, strong recommendations for penicillin prophylaxis were made only for those with HbSS disease and HbS-β^0 Thalassemia.[19] For those with other SCD forms, namely HbSC disease and HbS-β^+ Thalassemia, the summary puts forth a weak recommendation with low-quality evidence that clinicians consider not prescribing penicillin for infants and children who have not had splenectomy or IPD. However, the guidelines acknowledge that many clinicians do prescribe penicillin universally for those with all forms of SCD and generally recommend that consultation by an SCD specialist should guide care. In a subsequent review article on the prevention and management of infection in SCD, this was criticized as lack of strong support for universal penicillin prophylaxis in SCD by the NHLBI.[221] This review by Sobota et al. recommended

identical use of antibiotics in those with HbSC disease until further research determined the safety of doing otherwise.

Little research specific to forms of SCD beyond HbSS disease drives a lack of consensus regarding the prophylactic use of penicillin for SCD types outside of HbSS disease and HbS-β^0 Thalassemia.[19,33,222] Current guidelines for the management of these other forms of SCD have been generalized from studies either exclusive to or a majority of those with HbSS disease.[19] Both the PROPS I and PROPS II studies were performed in children with HbSS disease exclusively, for example.[5,219] The paucity of data comes from the lower prevalence of these other forms of SCD as compared to HbSS disease, which accounts for approximately 64% of hemoglobinopathies.[26] HbSC disease is the second most common form of SCD, yet it comprises only approximately 16% of hemoglobinopathies in the world.[26]

Data that are available indicates that in HbSC disease and HbS-β^+ Thalassemia, complications are typically less frequent and present later than in HbSS disease.[4,33,184] These have been considered to be more mild forms of SCD, and research suggests that the spleen typically remains unaffected for longer in individuals with these SCD forms.[41,223] Notably, this may allow for the development of humoral immunity and protection against fatal bacterial infection. One multi-centered, prospective study found that in their cohort of 201 patients with HbSC disease, none developed functional asplenia prior to age four. By 12 years old, 55% of the HbSC patients still had not demonstrated pathological splenic dysfunction.[224] Based on these findings, Lane et al. raised concerns that antibiotic use may be unnecessary in this population and in fact may hinder the natural acquisition of antibodies needed to confer protection later in life, when asplenia did appear to develop.[224] The findings are consistent with other studies, which indicate that the

susceptibility to infection in milder SCD forms follows a similarly delayed timeline.[179,225] This has led to questioning of the appropriateness of penicillin prophylaxis in these other SCD types.

One large epidemiological study in the DNC indicates that penicillin prophylaxis in these forms of SCD may not be necessary. In this cohort, children with HbSC disease and HbS-β^+ Thalassemia do receive penicillin prophylaxis. It is prescribed for those with HbSS disease and HbS-β^0 Thalassemia.[217] In a 2010 report on survival statistics in the cohort, which consists of 30.2% (284/940) individuals with HbSC disease, the four recorded deaths owing to pneumococcal sepsis that occurred between 1983 and 2007 were in individuals with HbSS disease and HbS-β^0 Thalassemia. None of the deaths in those with HbSC disease were determined to be related to SCD, and 98.4% of individuals with HbSC disease survived past age 18.[79]

5.1.6 Issues with Prophylaxis

Despite the enabling of penicillin prophylaxis and pneumococcal vaccination through NBS, remaining issues reduce its effectiveness. In their guidelines of SCD management, the NHLBI expert panel concedes that risk of pneumococcal infection remains a top concern in SCD primarily due to increasing emergence of resistant pneumococcal strains and inadequate immunization.[19]

Antibiotic Resistance: While the importance of penicillin for children with HbSS disease under age five is not debated, its use in situations where it is necessity is less clear and should be weighed against potential risks. Namely, excessive antibiotic use may encourage the emergence of antibiotic resistant pneumococcal strains. The prevalence of resistant pneumococcal strains does appear to be increasing.[226] One study of resistant strains in North America found an increase from

5% prevalence in 1989 to over 35% in 1997. One-quarter of strains isolated were moderately resistant, and 11% were found to be highly resistant.[227]

The emergence of resistant pneumococcal strains supports the discontinuation of penicillin once infection risk in SCD has subsided**.** Resistant strains not covered by penicillin or the current pneumococcal vaccination protocol lead to decreased effectiveness of the prophylactic measures relied on by high-risk populations, such as those with SCD prior to this age. A concerning trend of increasing incidence of IPD in those with SCD following introduction of the PCV7 and PCV13 vaccines has been a focus of recent studies. In 393 pneumococcal samples obtained from children with SCD in the eight years following PCV7 introduction, nearly 90% of isolated strains were not covered by either penicillin or the recommended vaccination course at the time.[228] In another study that looked at cases of IPD one decade after the introduction of the PCV7 vaccine, the frequency of IPD was found to have risen most significantly in the last two years of the study, indicative of an upward trend in infection rates.[229] The majority of IPD cases were found by this study to occur with serotypes not covered by penicillin or the PCV7 and PPSV23 vaccines. Finally, a 2014 review of literature published since the early 2000s presented a number of additional retrospective case review studies that demonstrated an increasing incidence of IPD in immune-compromised individuals in what the authors termed the post-PCV era.[230]

Immunization Compliance: Penicillin alone confers incomplete protection against IPD for children with SCD.[231,232] Pneumococcal immunization with both PCV13 and PPSV23 is integral to the prophylactic measures recommended by current guidelines.[19] These evidence-based guidelines additionally support the conditional discontinuation of penicillin in children with SCD over the age of five only in the case that complete pneumococcal vaccination can be assured.[19,216]

Consequently, insufficient or unverified pneumococcal immunization remains a barrier to appropriate discontinuation of penicillin.

A number of studies have found deficient vaccination rates in those with SCD, calling for strategies to improve these rates. In an audit of the immunization status of 58 individuals with SCD at an urban medical center, just over half (56%) of those with SCD had completed the recommended vaccination schedule for *S. pneumoniae*.[233] In another comparative study of patients with SCD who were seen at a hematology clinic between 2004 and 2009, only 21.5% were found to be vaccinated against pneumococcus upon admission.[234] Finally, a case-control study involving enrollees in Michigan Medicaid and Children's Special Health Care Services compared the pneumococcal vaccination rates in 179 patients with SCD born between 2001 and 2005 with 537 controls who did not have SCD. The controls were also Medicaid beneficiaries and were matched based on age, race, and county. While vaccination rates in the SCD cohort at every age group were significantly higher than the controls, they were lower than national averages, as reported in the National Immunization Survey data: 72% versus 84% at three months of age, 54% versus 74% at five months, and 73% versus 92% at 24 months. These rates were deemed by the study authors to be insufficient for the high-risk population of children with SCD. The authors, Nero et al., called for further studies to identify barriers to pneumococcal vaccination, so that successful interventions could be implemented to address under-vaccination in children with SCD.[235]

A variety of strategies have been investigated to increase vaccination adherence in the SCD population. These include provider and parent education, reminders provided by a patient navigator, and enhancements to the Electronic Health Record (EHR).[234,236] The latter has been the focus of a number of interventions, which have generally demonstrated promise in the ability of EHR technology to increase immunization rates.[234,236–238] In one case, Fiks et al. demonstrated in

their urban pediatric population that EHR-based clinical reminders significantly improved routine childhood vaccination rates by two years of age.[238] While this study was not specific to pneumococcal vaccination or SCD, the population possessed similar demographics, specifically a high percentage of minority patients (>80%) and of individuals with Medicaid coverage (>85%), that more closely pertains to the SCD population than to the more general population engaged by the National Immunization Study.[232] The EHR alert based intervention assessed by Fiks et al. increased routine pediatric immunization rates from 81.7% to 90.1% post-intervention.[238]

A 2015 interventional study conducted in a pediatric SCD clinic also leveraged the EHR system in its aim to increase influenza vaccination rates.[236] Focusing on the inaccessibility of influenza vaccination information in the EHR clinic note, the intervention revised the Sickle Cell Encounter Note to make the patients' immunization eligibility more prominent to allow for easier provider recognition during the clinic visit. It additionally integrated the clinic's Sickle Cell Registry into the EHR to enable targeting of the high-risk population. Following this quality improvement effort, influenza vaccination rates in the study's pediatric population significantly increased, from a rate of 45% to 71% ($p < 0.0001$). Although a number of strategies in addition to those involving the EHR were included in their intervention, Sobota et al. acknowledged the utility, relative simplicity, and inexpensiveness of the EHR improvements as a tool to increase in vaccine compliance rate.[236]

Finally, a 2016 Quality Initiative (QI) at an urban academic medical center in Philadelphia, Pennsylvania focused on the EHR to address inadequate adherence to pneumococcal vaccination in its immune-compromised population of children who had received kidney transplants.[239] The two vaccines of interest in the study are also those currently required for children with SCD: PCV13 and PPSV23.[209] Following a period of immunization record collection from outsides

sources, documents were scanned into the patients' charts, and PCV13 and PPSV23 immunization dates were entered into the immunization section of the EHR. A space for manual entry of the patients' PCV13 and PPSV23 vaccines was also added to the progress note template. Lastly, an algorithm for identification of vaccine candidates was created, so that an alert advising the provider to consider pneumococcal vaccination would be displayed on the progress note during their clinic visit. Progress was measured as a decrease in missed vaccine opportunities. A significant drop noted in the first six months of the QI, and at the end of their one-year evaluation period, the percentage of fully vaccinated patients had increased from 10% to 52%. However, the majority of this improvement was obtained in the first six months and was attributed primarily to the active efforts of the nurse to obtain records. It was noted that in absence of these dedicated staff hours, the rate of missed vaccine opportunities returned to baseline. Thus, continued active record collection was identified as a more crucial component of the intervention than EHR enhancements, which alone had minimal effect on sustained improvement of vaccination rates.[239]

5.1.7 Description of a Quality Initiative to Improve Appropriate Penicillin Prescription

The Pediatric Sickle Cell Clinic at University of Pittsburgh Medical Center (UPMC)-Children's Hospital of Pittsburgh (CHP) is one of six referral centers in Pennsylvania responsible for following up on positive NBS results for SCD. The Clinic is specifically responsible for newborns born in 19 different counties in the western portion of Pennsylvania. Each year, an average of 10 to 12 infants are born with SCD in its designated region. The Clinic currently follows conservative guidelines, prescribing penicillin to infants with all SCD disease types. After the age of five years old, the clinic seeks to discontinue penicillin for all patients given: 1) no personal history of IPD, 2) no surgical splenectomy, 3) at least one dose of both PCV13 and PPSV23

vaccines received, and 4) parental approval. Those who have received PCV7 in place of PCV13 must receive the latter vaccine to be considered up-to-date. Penicillin prescription may be discontinued at any time after the age of five years of age for whom the preceding criteria are met, and prophylaxis is no longer considered indicated.

In the spring of 2017, The Pediatric Sickle Cell Clinic at CHP identified concerns with inadequate documentation of PCV13 and PPSV23 vaccination in its active patient population. One consequence of insufficient vaccine documentation was an inability to discontinue penicillin prophylaxis for many of the clinic's patients over the age of five. A system for documenting vaccinations had been lacking since the medical records were gradually transitioned from paper to electronic health records beginning in the early 2000s. Several barriers to maintaining updated immunization status in the EHR were identified. These included a significant number of missing outside immunization records, poor integration into the EHR of the clinic's previously hand-written notes documenting immunization, and the lack of a standardized entry space in the EHR to note immunization status.

In May 2017, a Quality Initiative (QI) was implemented at the Pediatric Sickle Cell Clinic that focused on a manual effort to collect missing records as well EHR enhancements in order to address issues with immunization documentation. The long-term goal of the QI was to improve the clinical care of its pediatric SCD population through increasing pneumococcal vaccination and also decreasing inappropriate penicillin use. In the initial stage, the Sickle Cell Clinic Research Nurse Coordinator collected missing immunization records for all active patients from primary care providers, the Pennsylvania State Immunization Registry, and any additional outside sources as they were identified. All faxed records were placed in a binder to be referenced by the Pediatric Sickle Cell staff. This binder continued to be updated with new faxed immunization records

following the QI. In June 2017, enhancements were made to the EHR to facilitate immunization documentation. Specifically, clinic notes could now be entered into an electronic document with dedicated space to enter vaccination status, date of administration, and recommended action steps was added to the Sickle Cell Clinic Visit Note. This information was set to auto-populate with future clinic visit notes as well. Vaccination records that had been retrieved from the initial collection step of the QI were entered in this space in the EHR. A system to regularly forward these notes to the pediatrician was also implemented, in order to recruit additional efforts in maintaining immunization compliance in the sickle cell clinic's population.

Through these actions, patients eligible for either pneumococcal vaccination or penicillin discontinuation were identified. This was addressed at their following clinic visits. For those individuals of the appropriate age who had not yet received the PCV13 and/or PPSV23 vaccines, the clinic's providers discussed the vaccine with the patient and his or her parents or caregiver. Vaccinations were administered either in clinic or by their primary care provider per family choice and with consent. For those individuals for whom prophylaxis was no longer indicated, penicillin was discontinued if the family was in agreement. These actions steps were recorded in the Clinic Note.

5.1.8 Aims of the Quality Initiative Assessment

For those individuals with SCD who have no disqualifying medical history, current clinical guidelines recommend that penicillin prophylaxis be discontinued after the age of five years old, when it has been demonstrated to no longer confer significant protection against pneumococcal infection.[19] Up-to-date immunization, which currently consists of PCV13 and PPSV23, is required

prior to stopping penicillin. Incomplete or unverified vaccination is a barrier to appropriate cessation of prophylaxis.

While current literature generally supports that penicillin be stopped after the age of five years old, it inadequately addresses the clinical experience of implementing this recommendation. Specifically, limited data exist regarding strategies for achieving this current clinical recommendation. This assessment addresses this current deficit of the literature by describing and evaluating a QI project that was carried out in the SCD specialty clinic of an urban academic medical center with rural outreach to 18 additional counties, which had the goal of decreasing inappropriate penicillin prescription in its patients over five years old. As an evaluation of the effects of the QI on vaccination and penicillin prescription rates, this work builds on previous findings, which support the use of the EHR to enhance medical care in the SCD patient population. Specifically, this assessment aims to show that enhancements to the Sickle Cell Clinic Visit note, as housed in EHR, improve rates of vaccination documentation and compliance, and ultimately reduce excess penicillin prescription in the pediatric patient population.

As an evaluation of the QI, this assessment aims to:

1) Characterize the patient population engaged by the QI, who were those patients seen at the Pediatric Sickle Cell Clinic at UPMC-CHP during the 18 months that spanned the implementation and sustained evaluation period of the QI. Basic demographic and medical information of all patients seen by the clinic during this time will be gathered from electronic databases maintained by the Pediatric Sickle Cell Clinic at CHP. Descriptive statistics will be applied to this data in order to describe the study population, as it may specifically relate to the effectiveness of the QI.

2) Statistically measure the degree of change in PCV13 and PPSV23 vaccine documentation, as it was available at the date of the clinic visit via a retrospective chart review of the EHR and paper immunization records. Data will be analyzed in age-appropriate subsets of patients, according to the vaccine schedule recommended by the CDC, for change in documentation rates between those time periods spanning implementation of the QI.
3) Statistically measure the degree of change in PCV13 and PPSV23 vaccination rates via a retrospective chart review. Vaccination status at the date of the clinic visit will be recorded as reported by the most current medical records available at the time of data collection. Data will be analyzed in age-appropriate subsets of the patient population to assess for change in immunization rates over the four designated time periods of the study.
4) Statistically measure the degree of change in appropriate penicillin prescription in this patient population over the age of six years old. Appropriate penicillin prescription will be defined as its prescription for patients who do not meet the clinic's established criteria for stopping penicillin; it will additionally be defined as penicillin *not* being prescribed for patients who do meet the criteria for penicillin prescription. This data will be analyzed in two ways. First, criteria will be applied that require documentation of immunization at the date of the clinic visit for appropriate penicillin discontinuation. A second set of criteria will not incorporate vaccine documentation as a criterion. This will be done in order to isolate the effect that missing immunization documentation had on penicillin prescription.

Through Aims 2 through 4, it is expected that this assessment will show that the QI resulted in significant increases in the metrics of vaccine documentation, immunization compliance, and appropriate penicillin prescription. It is anticipated that a significant increase in all three described

rates will be seen in the time period that directly follows the QI, as compared to the baseline established prior to implementation of the QI. It is also anticipated that these increases will be sustained in the time periods following the QI. Ultimately, this assessment is anticipated to show that enhanced clinical care may be achieved through specific efforts to increase accessibility of immunization records, both through manual staff efforts as well as modifications of the EHR.

5.2 METHODS

This QI was submitted and approved by the UPMC Quality Initiative Review Committee under project identification number 1528 (Appendix J).

5.2.1 Data Collection

Data for this project were retrieved from two sources: Cerner, which is the EHR system of CHP, and the Sickle Cell Database (SCDB). The SCDB is an online database that contains information on all inactive as well as active patients with a diagnosis of SCD who have been seen by the Pediatric Hematology Department of CHP since 1999. Each patient is assigned a unique identifying number in the SCDB that is distinct from his or her Medical Record Number. A portion of the information in the SCDB is pulled automatically from Cerner; this includes patient date of birth, medical record number, race, ethnic background, and insurance coverage. Additional information is manually collected from Cerner and entered into the SCDB by clinic staff each fiscal quarter. This information includes the SCD genotype, dates of all clinic and Emergency

Room visits, in-patient admissions, and active prescriptions for penicillin and hydroxyurea for all patients active that quarter.

For this project, all Sickle Cell Clinic visits that occurred in four separate time periods were pulled from the SCDB. As the specific actions of the QI's intervention took place between May 1, 2017 and June 30, 2017, a time frame of February 1, 2017 through October 31, 2018 was designated to measure pre-intervention rates as well as data at several time periods following the QI intervention to assess initial impact and sustainability/further improvements over time. The four time periods were defined as Pre-Intervention (February and April 2017), Post-Intervention (July, August, and September 2017), Sustain 1 (January, February, and March 2018), and Sustain 2 (July, August, September 2018). All time periods were three months in length, with the exception of the Pre-Intervention time period. This period was two months in length as the data for this time period were previously collected for an initial assessment of the QI and additional data were not available.

Each routine Sickle Cell Clinic visit that occurred in the four time periods of the QI project provided one data point. A unique clinic visit was characterized by a patient name and visit date associated with a Clinic Note. All patients with clinic visits included in this dataset had a diagnosis of SCD confirmed at the clinic. Appointments pulled from the SCDB other than routine Pediatric Sickle Cell Clinic visits, such as those for transfusions or bone marrow transplant evaluations, were removed from the dataset.

A total of 527 routine clinic visits for 180 patients comprised the complete data set. 118 clinic visits were represented in the Pre-Intervention time period, 193 in the Post-Intervention time period, 135 visits in the Sustain 1 time period, and 120 visits in the Sustain 2 time period. A smaller dataset was generated from the complete dataset, where only one clinic visit per patient was

represented in each time period. In cases where there were multiple clinic visits in one time period for the same patient, the latest chronological clinic visit in the time period used. In this data set, there were 85 clinic visits in the Pre-Intervention time period, 121 clinic visits in the Post-Intervention time period, 103 clinic visits in the Sustain 1 time period, and 97 clinic visits in the Sustain 2 time period. In Aims Two through Four, parallel analysis for both the complete dataset and this smaller dataset were performed and compared in order to evaluate for the influence that multiple visits by the same patient had on the analysis.

For every patient in the complete dataset, age at clinic visit, insurance type, race, ethnicity, and SCD type were also obtained through the SCDB. Data pulled from the SCDB were exported into a Microsoft Excel spreadsheet and stored on a secure server maintained by CHP. The remainder of the data were manually collected from the EHR via a retrospective chart review by twelve members of the CHP clinic staff. Data for the Pre-Implementation time period were collected from clinic notes scanned into the Outpatient Documents section of Cerner. Data for the remaining three periods were collected from the new EHR Sickle Cell Clinic Note, which was a product of the QI. Once collection was complete, the combined data were reviewed by one individual to ensure that the coded variables had been recorded accurately and consistently across all twelve reviewers. Following this final review, patients' names were removed from the dataset used for analysis, while their unique identifying number from the SCDB remained.

5.2.2 Coded Variables

All data collected through manual review of the EHR Clinic notes were coded as categorical variables (Yes/No) for the purpose of this analysis.

PCV13 Documented: PCV13 vaccination status was recorded as documented ("Yes") for that clinic visit if that visit's clinic note verified that it either had not been administered or had been administered at that visit or at any time prior. If confirmation of vaccination status was not written in the clinic note or was noted as "pending," PCV13 vaccination status was recorded as not documented ("No"). Vaccination status noted to have been provided verbally by the patient without medical records was also coded as not documented ("No"). As PCV13 vaccination is not to be administered until after two months of age, individuals younger than this age were not included in the analysis of this variable.[209]

PPSV23 Documented: Similar rules were applied to the coding for PPSV23 vaccine documentation status. In this case, clinic visits of individuals who were under two years of age were not included in this analysis, as PPSV23 administration is not appropriate prior to this age.[209]

PCV13 Given: The PCV13 vaccine was recorded to have been given ("Yes") if at least one dose had ever been correctly administered prior to or on the date of the clinic visit. This criterion was retrospectively applied. Thus, if it were noted in a future clinic note that PCV13 vaccination had been administered on a date prior to the clinic visit date of analysis, the variable was coded as "Yes." During the final review process, the latest Sickle Cell clinic note was examined for vaccine status for those individuals for whom it had not yet been confirmed. This was done to obtain the most accurate vaccination status possible.

If PCV13 was noted to not have been administered or its administration could not be verified at the time of final data collection, PCV13 was recorded as Not Given ("No"). This variable was also recorded as "No" in the case that PCV13 was administered incorrectly, i.e. prior to two months of age or concurrently with the PPSV23 vaccine. Additionally, for individuals who had received PCV7 in place of PCV13, this variable was recorded as "No." PCV13 is the more

comprehensive pneumococcal conjugate vaccine introduced to replace PCV7, and the clinic seeks to administer PCV13 to those who had previously received PCV7. Only individuals over the age of two months old were included in analysis of this variable.

PPSV23 Given: Coding for administration of the PPSV23 vaccine was performed with the same criteria for that of PCV13. For PPSV23 administration, age appropriate analysis corresponded to individuals aged two years of age and older.

Invasive Pneumococcal Disease: This variable was coded as "Yes" if the Clinic Note documented a past medical history of IPD. It was coded as "No" if this medical history was not noted in the clinic note.

Surgical Splenectomy: This variable was coded as "Yes" if the clinic note documented a past medical history of surgical splenectomy. In all other cases, it was recorded as "No."

Parental Preference: If discontinuation of penicillin prescription was identified to be appropriate but was continued based on parental preference, this variable was coded as "Yes." Otherwise, it was coded as "No."

Penicillin Prescribed: Penicillin was recorded as prescribed ("Yes") if the patient was actively prescribed penicillin at the end of that clinic visit. This was indicated by the inclusion of penicillin on the active medication list for that clinic visit note and also noted in the space for "Functional Asplenia Risk Assessment" in the clinic visit note. In the case that these two sources were conflicting, it was noted by the reviewer. These cases were examined during the final data review, and the most likely scenario was recorded, with input from a sickle cell clinic provider. Individuals taking amoxicillin were also recorded as "Yes," as amoxicillin is prescribed for those with a penicillin aversion or allergy. For clinic visits where a prescription for penicillin was not

present in the clinic visit note, or it was noted as discontinued at that visit, this variable was recorded as penicillin not prescribed ("No").

Penicillin Prescribed Appropriately: To achieve the Fourth Aim, two additional variables were generated to reflect the appropriate prescription of penicillin: "Appropriate Penicillin Prescription: Documentation" and "Appropriate Penicillin Prescription: No Documentation." Both variables were coded as "Yes" when penicillin was prescribed at the clinic visit and it was indicated, or when penicillin was *not* prescribed at the clinic visit and it was *not* indicated. The two variables differed by the criteria used to determine whether or not prescription of penicillin was indicated. As the QI focused on age appropriate discontinuation of penicillin prophylaxis, analysis of this variable was restricted to those patients six years of age or older at the time of the clinic visit. While current recommendations are that penicillin be discontinued after age five, the Pediatric Sickle Cell Clinic interprets this to mean that penicillin discontinuation is appropriate any time between the age of five and six years old. Thus, penicillin prescription prior to the age of six was still considered to be appropriate for this QI project.

The first, "No Documentation" was coded as "Yes" when penicillin was prescribed at that clinic visit and one or more of the following criteria were met: 1) medical history of a disqualifying medical event (IPD or of surgical splenectomy), or parental preference to stay on penicillin, and 2) pneumococcal vaccination was not complete. This variable was also coded as "Yes" when penicillin was not prescribed at that clinic visit and the following criteria were met: 1) no medical history of a disqualifying medical event (IPD or of surgical splenectomy) and no parental preference to stay on penicillin, and 2) pneumococcal vaccination was complete (Figure 4).

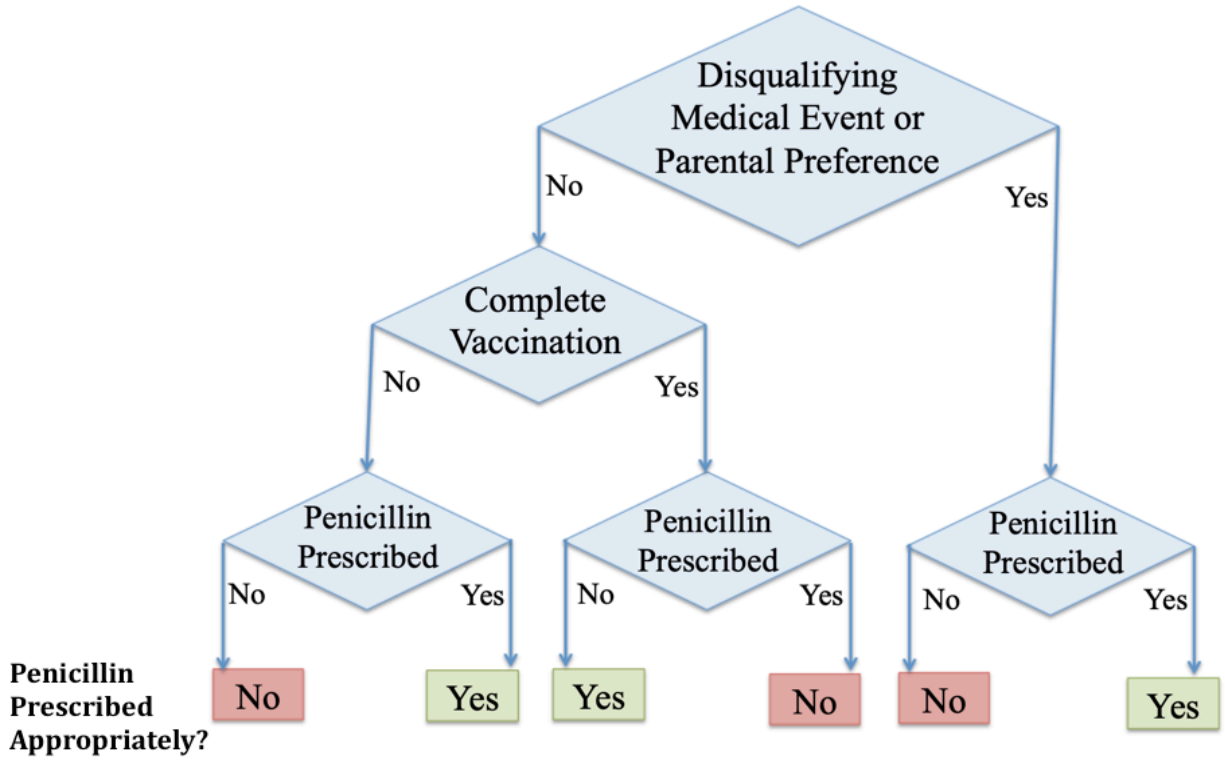


Figure 4. Flowchart for "No Documentation" Criteria

The second variable, “Appropriate Penicillin Prescription: Documentation,” differed from the first through the addition of an extra criterion: whether or not vaccination was completely documented at the relevant clinic visit (Figure 5). Because vaccine status was retrospectively applied, the previous variable (No Documentation) was not based on what was known at the time of the clinic visit when penicillin was being prescribed. This second variable used criteria that evaluated whether or not penicillin was appropriately prescribed given knowledge that was accessible in the medical records at the time of that clinic visit. Comparison of these two variables allowed for an evaluation of the proportion of penicillin prescription resulting from missing vaccination documentation.

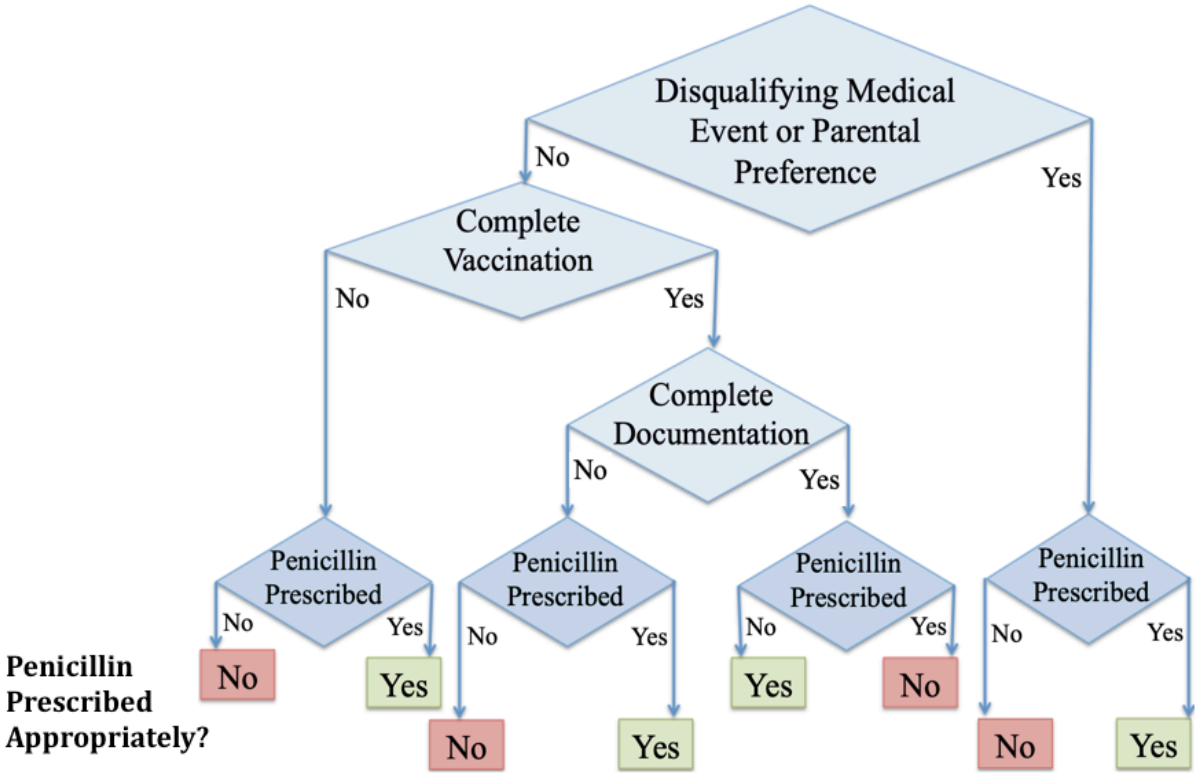


Figure 5. Flowchart for "Documentation" Criteria

5.2.3 Data Analysis

Data analysis was performed using Microsoft Excel and RStudio for Mac Version 1.1.456. Descriptive statistics were used to characterize the demographics of the intervention's population (Aim 1). Chi-squared analysis was performed to compare rates of vaccine documentation (Aim 2), vaccine administration (Aim 3), and appropriate penicillin prescription (Aim 4) across the four different time periods. A p-value under 0.05 was used to define statistical significance.

5.3 RESULTS

5.3.1 Aim 1: Description of the Patient Population

A total of 180 patients with a confirmed diagnosis of SCD were seen for 527 routine appointments at the Pediatric Sickle Cell Clinic at CHP in the four time periods that comprised the time period used to assess the QI (Table 9). The mean±SD age of patients taken at the midpoint of the year was 10.5±6.2 years (range 0.15 to 21.4 years). 73.3% (132/180) were above the age of six, the age by which penicillin was to be discontinued. The majority of patients identified as African American (97.2%, 175/180) and received Medical Assistance (84.4%, 152/180).

More patients were affected by an SCD type categorized as severe (61.1%, n = 102), designated here as HbSS disease and HbS-β^0 Thalassemia, as compared to all other SCD types (38.8%, n = 70). The most common SCD form was HbSS disease, with 57.2% (103/180) of the patient population, followed by HbSC disease with 32.8% (59/180). Smaller proportions of patients had HbS-β^+ Thalassemia (5%, 9/180) and HbS-β^0 Thalassemia (3.9%, 7/180). Additionally, there was one patient each (0.6%) with HbSE disease and HbS-Hereditary Persistence of Fetal Hemoglobin (HbS-HPFH). Three (1.7%) patients had a medical history of IPD. Twenty-two (12.2%) patients had received a surgical splenectomy.

Table 9. Demographics of the Patient Population

	Severe SCD Types[1]	Other SCD Types[2]	Total
Age			
Mean ± SD	9.1±6.0	11.6±6.3	**10.5±6.2**
Range	0.15-20.89	0.25-22.45	**0.15 – 21.4**
Under age 6	28.2% (31)	24.3% (17)	**26.7% (48)**
Sex			
Female	48.1% (53)	41.4% (29)	**45.6% (82)**
Male	51.8% (57)	58.6% (41)	**54.4% (98)**
Race			
Asian	0.9% (1)	1.4% (1)	**2.0% (2)**
African American	97.2% (107)	97.1% (68)	**97.2% (175)**
White	2.0% (2)	1.4% (1)	**1.7% (3)**
Ethnicity			
Hispanic/Latino	0.9% (1)	3.1% (2)	**98.3% (177)**
Not Hispanic/ Latino	99.1% (109)	96.9% (68)	**1.7% (3)**
Insurance			
Private	13.6% (15)	15.7% (11)	**14.4% (26)**
Medical Assistance	85.5% (94)	82.3% (58)	**84.4% (152)**
No Insurance	0% (1)	1.4% (1)	**1.1% (2)**
Total	0.9% (110)	97.1% (70)	**180**

[1] SCD types HbSS disease and HbS-β^0 Thalassemia
[2] SCD types HbSC disease, HbS-β^+ Thalassemia, HbSE Disease, and HbS-HPFH

5.3.2 Aim 2: Immunization Documentation

PCV13 documentation rates were analyzed for patients two months of age or older at the date of their clinic visit, as according to the appropriate time course for PCV13 administration. As measured by percent clinic visits with PCV13 status documented in the clinic note, the PCV13 documentation rate was 7.7% (9/117) at baseline. This corresponds to over 90% of clinic visits during the Pre-Intervention period that were missing documentation of whether or not the patient had received at least one dose of the PCV13 vaccine. Immediately following implementation of the QI, PCV13 documentation rate increased to a rate of 85.1% (160/188). This change between the Pre-Intervention and Post-Intervention time periods was found to be highly significant, as measured by chi-squared analysis ($p < 0.001$, Table 10). Documentation rates continued to increase in the three time periods that followed the QI. Specifically, PCV13 documentation was confirmed for 85.1% (160/188) of clinic visits in the Post-Intervention period, 89.6% (120/134) in the Sustain 1 period, and 96.7% (116/120) in the Sustain 2 period (Table 10, Figure 6). The change in documentation rates achieved between baseline and the final period of this project's assessment (Sustain 2) was 89%; this change that was also found to be highly statistically significant ($p < 0.001$).

PPSV23 vaccine documentation rates demonstrated a similar pattern over the project's time course. At a rate of 81.4% (131/161), PPSV23 documentation Post-Intervention was significantly greater compared to the Pre-Intervention rate of 10.5% (11/105, $p < 0.001$) (Table 11). Documentation rates continued to increase in the time periods that followed the QI. In the two final periods, PPSV23 status was documented for 87.2% (96/110) of clinic visits in the Sustain 1 period and for 94.0% (94/100) in the Sustain 2 period. PPSV23 vaccine documentation rates

increased by 83.5% between the Pre-Intervention and Sustain 2 time periods, which is highly significant ($p < 0.001$).

Complete ("Up-to-Date") vaccination documentation status rates were defined differently depending on age and CDC immunization guidelines: for individuals between two months and two years old, complete vaccination documentation was considered as having PCV13 status documented at least once, and for individuals older than two years old, both PCV13 and PPSV23 statuses needed to be documented at the date of the clinic visit. This rate increased as well, paralleling those of the individual vaccine documentation rates. The baseline complete documentation rate was 6.8% (8/117) of all clinic visits in the Pre-Intervention time period. Following the QI, this rate increased to 81.4% (153/188) of clinic visits in the Post-Intervention period, 86.6% (116/134) in the Sustain 1 period, and 94.2% (113/120) in the Sustain 2 period (Table 10, Figure 6). Consistent with the other vaccination documentation findings, a significant increase in complete pneumococcal vaccine documentation was demonstrated between the Pre and Post-Intervention time periods ($p < 0.001$), as well as between the first and last time points measured in this QI project ($p < 0.001$). Specifically, we found an increase of 74.6% more clinic visits with complete pneumococcal vaccination documentation between the Pre-Intervention and Post-Intervention time periods, and an increase of 87.4% was found between Pre-Intervention and the final time period, Sustain 2.

Table 10. Vaccine Documentation Rates by Time Period

Time Period	Documentation Rate		
	PCV13	PPSV23	Complete
Pre-Intervention	7.7% (9/117)	10.5% (11/105)	6.8% (8/117)
Post-Intervention	85.1% (160/188)	81.4% (131/161)	81.4% (153/188)
Sustain 1	89.6% (120/134)	87.2% (96/110)	86.6% (116/134)
Sustain 2	96.7% (116/120)	94.0% (94/100)	94.2% (113/120)

Table 11. Change in Vaccine Documentation Rates Across Time Periods

Vaccine	Time Periods	N	DF	Chi-Square	P-value
PPSV23	1 versus 2	305	1	171.8	<0.001*
	1 versus 4	237	1	184.6	<0.001*
PCV13	1 versus 2	266	1	125.5	<0.001*
	1 versus 4	205	1	139.7	<0.001*
Both	1 versus 2	305	1	157.8	<0.001*
	1 versus 4	237	1	177.3	<0.001*

Time Periods: 1: Pre-Intervention; 2: Post-Intervention; 3: Sustain 1; 4: Sustain 2
** Statistically significant change*

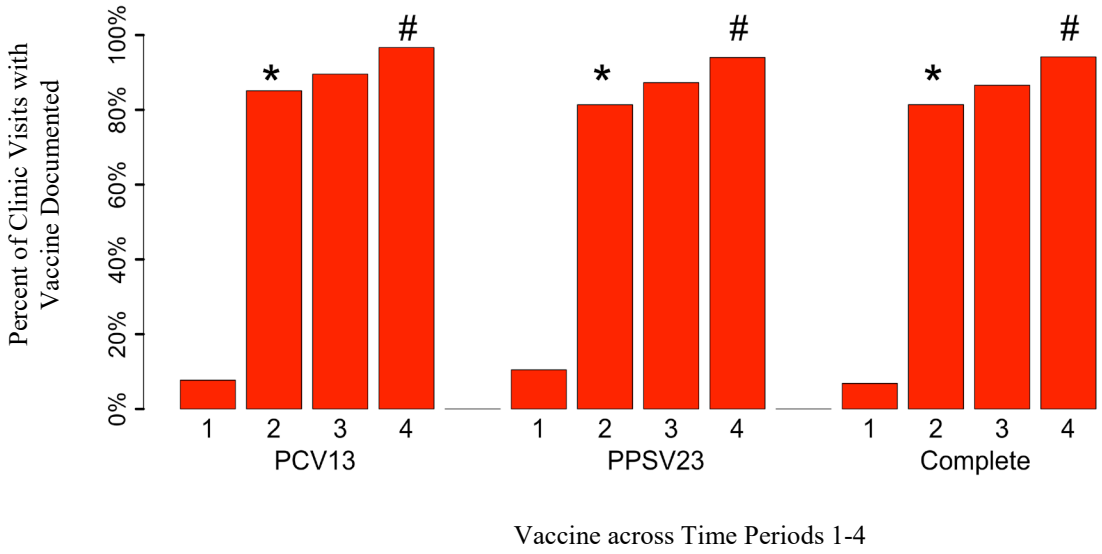


Figure 6. Vaccine Documentation Rates by Time Period

Vaccine Documentation rates, as recorded in the Sickle Cell Clinic Notes, across the four time periods (1: Pre-Intervention; 2: Post-Intervention; 3: Sustain 1; 4: Sustain 2). Analysis was restricted to children over the age of two months old for both PCV13 and Complete Documentation, and to children over the age of two years old for PPSV23 status. For all three metrics (PCV13, PPSV23, and Complete Documentation), significance was found in documentation rates between Pre-Intervention and Post-Intervention, as well as between the three periods that followed the QI (Post-Intervention, Sustain 1, Sustain 2).
** $p < 0.001$: Pre-Intervention versus Post-Intervention*
 # $p < 0.001$: Pre-Intervention versus Sustain 2

5.3.3 Aim 3: Immunization Rate

Analysis of pneumococcal vaccination rates was performed using the same age-specific data subsets that were used for vaccination documentation. These were determined according to the immunization schedule as published by the CDC.[209]

A 10.3% increase in PCV13 immunization rates occurred across the four time periods analyzed for this QI project. The Pre-Intervention rate of 75.2% (88/117) increased to 85.8% (103/120) by the final time point, Sustain 2 (Table 12, Figure 7). However, PCV13 immunization rates did not show a consistent increase across the four time periods. PCV13 immunization rates increased to 84.1% (158/188) Post-Intervention, decreased to 79.1% (106/134) in the subsequent

time period (Sustain 1), and rose again in the final time period (Figure 7). The change in PCV13 vaccination rates as not found to be significant when measured between the Pre-Intervention and Post-Intervention time periods ($p = 0.080$), as well as between the Pre-Intervention and Sustain 2 periods ($p = 0.057$, Table 13)

PPSV23 vaccination rates continually increased across all four time periods yet remained consistently lower than PCV13 vaccination rates in the corresponding time periods. The baseline rate for PPSV23 vaccination was 58.1% (61/105) in the Pre-Intervention time period, grew to 66.5% (158/188) Post-Intervention, and continued to increase to 73.6% (81/110) in the Sustain 1 and 81.0% (81/100) in the Sustain 2 time periods. The change in PPSV23 vaccination rates between the Pre-intervention to Post-Intervention time periods (8.4%) was not statistically significant ($p = 0.21$). However, the PPSV23 immunization rates significantly increased between the baseline and final time point ($p < 0.001$). As it was measured between the Pre-Intervention and Sustain 2 time periods, the total change in PPSV23 vaccination rates over the total time course of this QI project was 22.9%.

Complete vaccination rates were determined similarly to complete documentation rates, as previously described in Aim 2. Vaccination was considered to be complete as long as one dose of PCV13 had been documented as appropriately administered to children between two months old and two years old, and one dose each of PCV13 and PPSV23 had been documented as appropriately administered to children two years of age and older. This rate increased across the four time periods: Pre-Intervention: 54.7% (64/117); Post-Intervention: 63.8% (120/188); Sustain 1: 67.9% (91/134); Sustain 2: 75.0% (90/120). While the initial increase in rates from Pre-Intervention to Post-Intervention was not significant, ($p = 0.14$), a significant change was found between the first and final time periods of this project ($p = 0.002$).

Table 12. Pneumococcal Vaccination Rates by Time Period

Time Period	Immunization Rate		
	PCV13	PPSV23	Complete
Pre-Intervention	75.2% (88/117)	58.1% (61/105)	54.7% (64/117)
Post-Intervention	84.0% (158/188)	66.5% (107/161)	63.8% (120/188)
Sustain 1	79.1% (106/134)	73.6% (81/110)	67.9% (91/134)
Sustain 2	85.8% (103/120)	81.0% (81/100)	75.0% (90/120)

Table 13. Change in Pneumococcal Vaccination Rates Across Time Periods

Vaccine	Time Periods	N	DF	Chi-Square	P-value
PPSV23	**1 versus 2**	305	1	3.06	0.080
	1 versus 4	237	1	3.62	0.057
PCV13	**1 versus 2**	266	1	1.57	0.210
	1 versus 4	205	1	11.57	<0.001*
Both	**1 versus 2**	305	1	2.14	0.140
	1 versus 4	237	1	9.85	0.002*

Time Periods 1: Pre-Intervention; 2: Post-Intervention; 3: Sustain 1; 4: Sustain 2
** Statistically significant change*

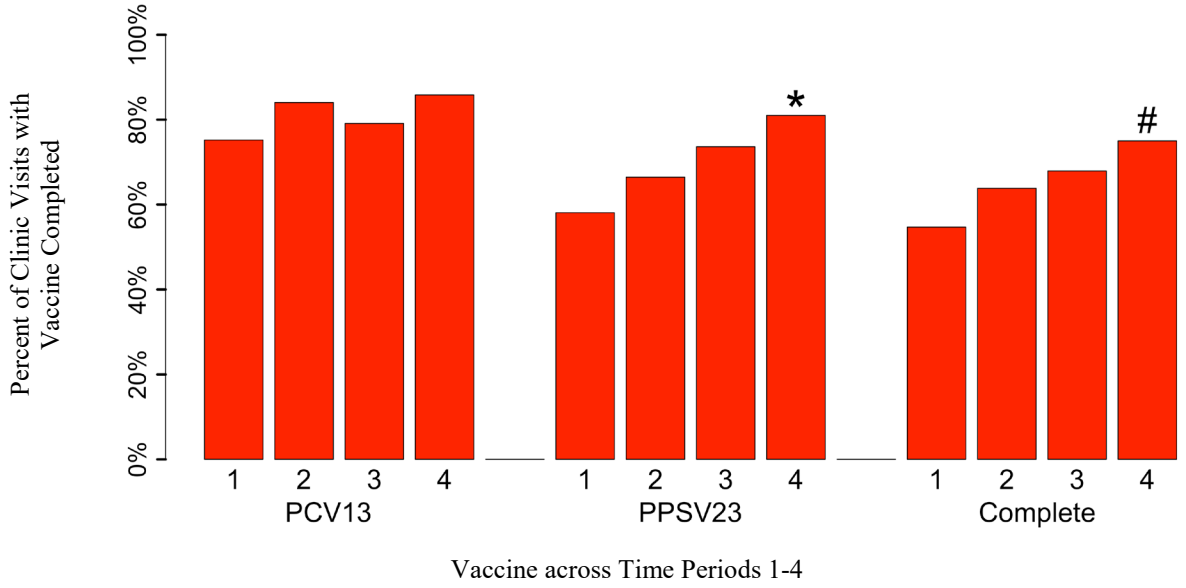


Figure 7. Pneumococcal Vaccination Rates by Time Period

Pneumococcal vaccination rates by time period (1: Pre-Intervention; 2: Post-Intervention; 3: Sustain 1; 4: Sustain 2). Analysis was restricted to children over the age of two months old for both PCV13 and Complete Vaccination, and to children over the age of two years old for PPSV23 status.
** $p < 0.001$: Pre-Intervention versus Post-Intervention*
 # $p < 0.05$: Pre-Intervention versus Post-Intervention.

5.3.4 Aim 4: Appropriate Penicillin Prescription

As it relates to the final aim of this QI project, rates of appropriate penicillin prescription were examined across the four time periods. Analysis was limited to patients who were at least six years of age at their clinic visit date, as this is the age at which penicillin prophylaxis could be appropriately stopped if all discontinuation criteria were met.

When immunization documentation status was included in the criteria for appropriate discontinuation of penicillin ("Documentation"), the Pre-Intervention rate of appropriate penicillin prescription was determined to be 54.1% (46/85) (Table 14). This translates to 45.9% of clinic visits where penicillin was prescribed for patients for whom it was not indicated. While a lack of penicillin prescription when it was indicated would qualify as inappropriate penicillin prescription,

this situation did not represent any actual cases in this data set (n = 0). For all patients for whom penicillin was indicated, it was prescribed.

Under the second set of criteria ("No Documentation"), vaccine documentation status at the date of the clinic visit was not a factor in determining whether or not penicillin prescription was appropriate. This allowed for a retrospective analysis of whether or not penicillin prescription would have been appropriate had vaccine documentation been complete at the clinic visit. In this case, a lower rate of appropriate penicillin prescription was found, as would be expected under these more stringent criteria. Pre-Intervention, 34.1% (29/85) of clinic visits were found to have appropriate prescription of penicillin. This means that in the majority of visits, penicillin was being inappropriately prescribed.

Under both criteria, the rates of appropriate penicillin prescription significantly increased in the Post-Intervention time period (Figure 8). Under the criteria that considered documentation, appropriate prescription rates increased from 54.1% to 82.7% ($p < 0.001$) (Table 15). Applying the retrospective criteria ("No Documentation"), rates increased from 34.1% to 79.7% ($p < 0.001$). Under both criteria, appropriate penicillin prescription continued to increase across the time periods and was appropriately prescribed at an identical rate of 94.0% (78/83) in the final time period of this QI project (Sustain 2). This represented a statistically significant change in rates of appropriate penicillin prescription under both criteria ($p < 0.001$).

Table 14. Appropriate Penicillin Prescription Rate by Time Period

Time Period	Prescription Rate	
	Documentation	No Documentation
Pre-Intervention	54.1% (46/85)	34.1% (29/85)
Post-Intervention	82.7% (110/133)	79.7% (106/133)
Sustain 1	90.1% (86/95)	89.5% (85/95)
Sustain 2	94.0% (78/83)	94.0% (78/83)

Table 15. Change in Appropriate Penicillin Prescription Rate Across Time Periods

Criteria	Time Periods	N	DF	Chi-Square	P-value
Documentation	**Pre-Intervention versus Post-Intervention**	218	1	43.79	<0.001*
	Pre-Intervention versus Sustain 2	168	1	19.45	<0.001*
No Documentation	**Pre-Intervention versus Post-Intervention**	218	1	62.50	<0.001*
	Pre-Intervention versus Sustain 2	168	1	65.50	<0.001*

* *Statistically significant change*

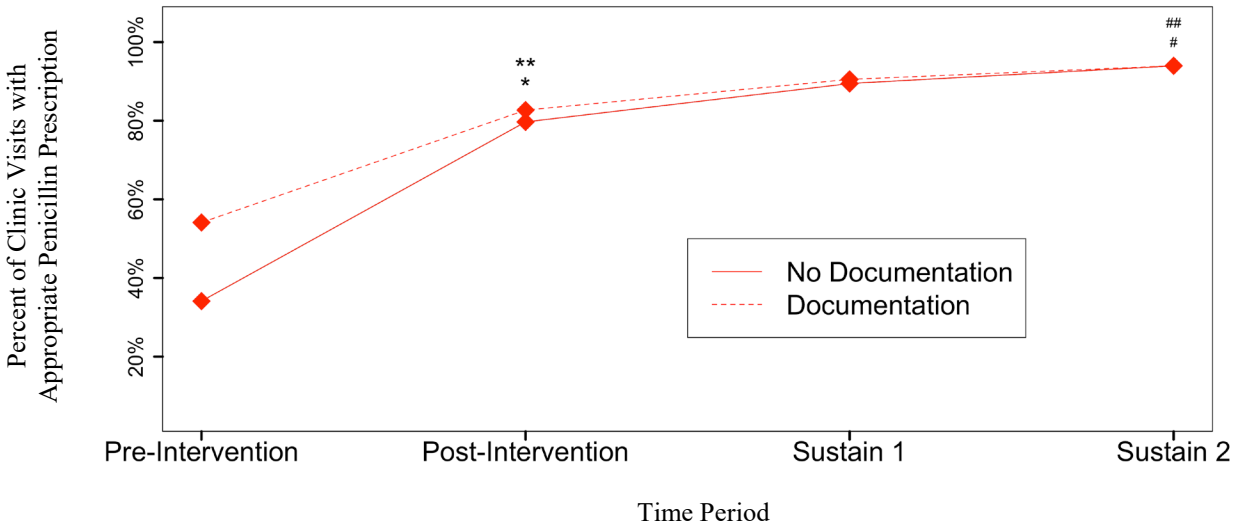


Figure 8. Appropriate Penicillin Prescription Rates Across Time Periods

Percent clinic visits with appropriate use of penicillin across the four analyzed time periods. The solid line represents the application of retrospective analysis ("No Documentation"), while the dashed line represents the medical history information that was currently available at the date of the clinic visit ("Documentation").
** p < 0.001: Pre-Sustain versus Post-Sustain, "Documentation"*
 # p < 0.001: Pre-Intervention versus Sustain 2, "Documentation"
*** p < 0.001: Pre-Sustain versus Post-Sustain, "No Documentation"*
p < 0.001: Pre-Intervention versus Sustain 2, "No Documentation"

5.4 DISCUSSION

The results of this assessment demonstrate that a QI focused on increasing documentation of pneumococcal immunization can lead to improvements in penicillin prescription in a pediatric sickle cell clinic. More broadly, it suggests how a modification of the EHR that increases access to important information during clinic visits may improve care. While previous research has explored the use of the EHR to increase vaccination rates, this report on a QI project is the first, to our knowledge, to show how utilization of the EHR may contribute to more judicious use of antibiotics in the SCD population.[236,238] As penicillin prophylaxis for SCD is universally

implemented in the United States via NBS, this assessment, which focuses on a strategy to discontinue penicillin use when it is no longer recommended, has implications for public health.

In the second aim, this assessment found that documentation of pneumococcal immunization status in the EHR significantly increased after a QI that involved: 1) staff time dedicated to collecting outside records, 2) the creation of a centralized source for storing paper records, and 3) enhancements to the EHR Sickle Cell Clinic Note. The rate of clinic visits with complete immunization documentation was less than 10% in the Pre-Intervention time period and grew to 81.3% post-intervention. A continued increase in documentation rates over the one year that followed the intervention was also demonstrated. This finding supports this strategy's ability to sustainably improve immunization documentation in the medical records of SCD patients.

The increase in documentation rates that immediately followed the intervention is consistent with findings of similar interventions. In their evaluation of a QI to improve pneumococcal vaccine rates in an immuno-compromised pediatric population, Malone et al. found that vaccination rates significantly increased after staff hours were allocated for requesting missing records.[239] In the absence of this dedicated time, however, their progress metric returned to baseline over the following year. While this project similarly demonstrated significant improvements in its goal immediately following the intervention, the improvement was sustained and increased over the year of analysis.

Several reasons may explain the discordance between these two studies' findings regarding the sustainable effect of a QI that prominently featured staff efforts for record collection. Most notably is the difference in what was measured and analyzed. Malone et al. examined the percent of clinic visits for which the opportunity for immunization was not missed; whereas in the case of this assessment, progress was first measured by the change in proportion of clinic visits with

verified pneumococcal vaccination documentation. This assessment's initial progress measure is more directly related to the clinical nurse's efforts of collecting records. Additionally, the progress measure used by Malone e al. was a measure of incidence. On the other hand, this intervention's progress measure was cumulative in nature: Once documentation is obtained for a patient, it will hopefully continue to be present in all subsequent visits as long as the current clinic procedures are followed. This is a specific feature of the Sickle Cell Clinic note. A more universal means of creating a lasting record of immunization status would be to upload immunization updates to the state immunization website. Of note, as the majority of patients were represented at least twice in the dataset across the four time periods, use of this measure likely exaggerates the true ongoing improvements that can be attributable to this intervention. Additionally, the effort to collect immunization records that occurred during the dedicated staff time was made for all active patients in the clinic. If a patient whose records were successfully obtained during the initial staff effort of record collection was not seen until a later time period of the evaluation, this delay would inaccurately convey a sustained effect of the initial intervention. However, continued effort is needed to enter this data into the patient's EHR at the later date it is received. Finally, the continued increases in documentation rates likely reflect the impact of time. As obtaining records often required sending multiple fax requests to outside medical systems and waiting for records to be returned, documentation rates are expected to increase over time, as was seen in Aim 2.

The demonstrated continued increase in documentation rates is unlikely to be solely due to the two-month effort by the Sickle Cell Clinic nurse, however. As not all missing records were identified and collected during the two months of the intervention, the findings do support a sustained ability to obtain immunization records. Additionally, as the Sickle Cell Clinic at CHP is the region's SCD specialty clinic, it sees all newborns identified through NBS, as well as

individuals with SCD who move to the region. These are both sources of new patients. Patients coming from external medical systems are more likely to be missing records and have medical records that are more difficult to obtain. Thus, an ability to not only sustain, but increase immunization status documentation in the clinical note over time indicates that the other components of the intervention, such as the enhancements to the EHR, also positively impacted documentations rates. To more fully understand the sustained impact of the intervention on vaccine documentation, later times points need to be assessed.

As another goal of the QI, pneumococcal vaccination rates increased over the time analyzed by this assessment. This increase, as measured in Aim 3, was found to be statistically significant for PSV23 status as well as complete pneumococcal vaccination status. Baseline immunization rates in the Pre-Intervention time period were measured to be 58.1% for PPSV23 and 54.7% for complete vaccination; this increased to 81.0% for PPSV23 and 75% for complete vaccination in the final time period evaluated.

The Pre-Intervention PCV13 immunization rate of 75.2% demonstrated here is consistent with the 73% rate of PCV13 immunization found by Nero et al in the Michigan pediatric SCD population at 24 months of age.[232] While this current assessment identified documentation, rather than immunization, as a larger barrier to discontinuing penicillin at an appropriate age, its findings of a baseline pneumococcal vaccination rate similar those of Nero et al support the conclusion made by Nero et al., that the SCD population in the United States is under-vaccinated. This conclusion was based on findings of vaccination rates that were significantly lower than national averages in the respective age groups. However, Nero et al. found vaccination rates of children with SCD to be higher than those rates in age, race, and geography-matched controls. Race-based health disparities in the United States are well-documented, and such lower rates of immunization

found by Nero et al. supporting race and geography-based barriers to immunization are consistent with this.[139] Of note, immunization status evaluated by Nero et al., pertained only to the PCV13 vaccine. In this assessment, the baseline documented PPSV23 and complete vaccination rates were lower than those of PCV13, at 58.1% and 54.7% respectively. While results of this QI demonstrated that true vaccination rates are likely to be higher than what is reflected in the medical documentation, this further indicates that children with SCD may be insufficiently protected against pneumococcal infection.

In light of inadequate documented baseline immunization rates, this assessment demonstrated an ability of the QI to significantly increase these rates by an average of approximately 18% between the initial and final time points. This is consistent with other QI interventions described in the literature.[234,236,238] Thus, this assessment adds to this body of work, which suggests that use of the EHR to increase visibility of vaccine status during clinic visits and assist with identifying eligible patients can significantly improve immunization rates. Given the populations of this along with the other studies, these findings may hold particular relevance for urban and/or high-risk populations.

Documentation of PPSV23 vaccination rates remained lower than PCV13 rates throughout the time span of this project's assessment. The PPSV23 vaccine has been approved by the FDA since 1983, while PCV13 was not introduced until 2010.[212] One concern of the clinic was that older patients lacked PCV13 coverage, due to having received the PCV7 vaccine in its place and then not receiving the PCV13 when it became available. PCV13 vaccination rates that exceeded PPSV23 may also be explained by the prioritization of PCV13 in individuals who were in need of both. This prioritization is a result of two factors: first, PCV13 confers superior protection against pneumococcal infection, and second, PPSV23 may be administered sooner after PCV13

administration (2 months) than vice versa (12 months). Additionally, as different age criteria apply to the two vaccines, the age composition of the patient populations analyzed for PCV13 and PPSV23 immunization status differed. Age or another related characteristic may be confounding the results. It may indicate that older individuals may be less likely to be adequately immunized. This could be explored in further research. Finally, the measure of vaccination status used in this assessment was not direct. Its accuracy is limited by what information was available in the most current clinic note. As the vaccine was not noted to have been received if relevant records were never obtained, the findings in Aim 3 finding likely reflects incomplete documentation, in addition to actual vaccination rates. However, as is demonstrated in Aim 2, the differences in documentation rates of the PPSV23 and PCV13 vaccines were minimal and are unlikely to fully account for the differences found in PCV13 and PPSV23 vaccination rates.

As the ultimate goal of the QI, this assessment aimed to demonstrate how efforts to increase pneumococcal immunization documentation and compliance rates may affect appropriate penicillin prescription in the pediatric SCD population. The results of Aim 4 support that such an intervention has a positive effect on appropriate prescription, which for the purpose of this assessment, was defined as its prescription when indicated and a lack of its prescription when not indicated. In review of the final data, inappropriate penicillin prescription was only represented by cases of excessive penicillin prescription; this is when penicillin was prescribed despite clinical guidelines that suggest that penicillin is no longer necessary. In no cases was penicillin not prescribed despite being indicated, which is reassuring given the strong recommendation for penicillin prophylaxis by the NIH guidelines that is based on the PROPS study.[19]

Prior to the intervention, penicillin was appropriately prescribed to the clinic's patients over six years old in 54.1% of clinic visits when using criteria considered immunization

documentation. This rate was just over one-third of clinic visits (34.1%) when retrospective criteria were applied. While the former criteria reflect the actual clinical requirements for penicillin prescription, the latter set of criteria was used to emphasize the effect that missing documentation had on unnecessary penicillin use. The difference between these rates, which was 20.0% at baseline, represents the minimum rate of inappropriately sustained penicillin prescription that can be attributed to the immunization documentation missing in the EHR. The strength of the intervention's effect on immunization documentation is illustrated by a convergence of these two criteria's rates across the four time periods. By Sustain 2, the two rates were equal, which suggests that this QI removed missing records as a barrier to appropriate use of penicillin, although this may also be related to an artifact of data collection. This final rate was significantly higher (94.0%) than either baseline rate but was not 100%. This illustrates the role of other factors, such as discussing stopping penicillin with eligible patients, in prescribing penicillin appropriately. An evaluation of additional barriers, as well a direct analysis of the effect that insufficient pneumococcal immunization has on penicillin prescription, is a potential topic for future studies.

5.4.1 Limitations

A significant limitation of this assessment was its reliance on indirect means of measuring key variables, namely vaccination status and disqualifying medical events. Data for these variables were obtained from the patients' medical records. A fact that was central to this intervention is that medical records may be contradicting, incorrect, or not up to date. The data analyzed here can only be as accurate as its EHR source

The possible human error involved in collecting and recording this data introduces an additional potential source of error. A number of steps were taken to minimize possible sources of

inaccuracy. Immunization status was obtained from the latest Sickle Cell clinic note and applied retrospectively to clinic visits of previous time periods if it been missing from those clinic notes. This was done in order to most accurately reflect this variable of vaccination status for all data points. Additionally, cases with unclear notes regarding penicillin prescription were reviewed a second time by a separate reviewer. This individual also performed a final review of the collated data for inconsistencies and ambiguous data points and referred back to the clinic note for the most likely scenario. In spite of these efforts, immunization statuses likely remain underestimates of the true rates, because in the case of insufficient documentation, the vaccine was marked as not received. This is supported by the difference between documentation rates and actual immunization rates seen in Aims Two and Three, where many more patients had received the vaccine than was indicated by their medical records. Finally, only the clinic visit notes being reviewed for data collection were used to determine if the patient had experienced a disqualifying medical event (surgical splenectomy or IPD). Any such events that were not documented in the clinic visit note, but had occurred and were dictating penicillin prescription, would lead to a greater calculated rate of inappropriate penicillin prescription.

An additional limitation of this assessment has already been discussed in relation to Aim 2: the use of prevalence, rather than incidence, measures to evaluate for effects of the intervention. The presence of the same patients multiple times in the dataset means that both previous and new cases were evaluated for the audited time periods. As all of the variables were chronic in nature, a change made in a patient's vaccination, vaccine documentation, or penicillin prescription status that was brought about by the intervention was reflected in all subsequent data points for that patient. Using an incidence metric as did Malone et al., would add additional valuable insight into

effect of the QI. However, this metric would have less statistical power and would also not have allowed for analysis of the sustained effect of the QI for individual patients.

One hundred eighty patients were represented in the sample population. In 2017, the SCDB records the Sickle Cell clinic as having 221 active patients. At approximately 80% of the total patient population, this is a sufficiently large sample size to be considered representative. There is still a possibility for sampling bias. Many patients in the dataset are represented by more than one data point per time period. Patients with more data points are those who visited the clinic more frequently during the audited time period; they are also likely to be those who visit the Sickle Cell clinic more often than the average patient in general. These patients may differ in ways that make them not representative of the total pediatric patient population seen by the Sickle Cell Clinic. As these characteristics may relate to the probability of having pneumococcal vaccines documented or received, or to the other criteria used to determine penicillin prescription, such as history of a surgical splenectomy, this may have introduced systematic error into the way the three metrics of this QI's success were measured.

To analyze for the effect of this, a smaller dataset with each patient represented once per time period was analyzed in parallel to the larger dataset, as described in the methods section. A comparison of the two indicated a minimal effect of duplicate or triplicate patient visits in sample, with similar patterns and rates of improvement across the four time periods demonstrated by both datasets. Consequently, the larger dataset was utilized for this assessment. This choice was validated by Malone et al, who also used individual clinic visits, rather than unique patients, to analyze the effect of a QI with a similar structure and goal.[239]

It should be noted that the clinic, which is located in an urban center, is a specialty center that draws upon a large and diverse geographical area of patients in the western Pennsylvania

region. The unique characteristics of the pediatric Sickle Cell Clinic at CHP may indicate limitations of this QI's effectiveness to wider use, such as in primary care, non-academic, and/or rural care facilities. However, as described in Aim 1, the general demographic characteristics of the patient population seen at the Pediatric Sickle Cell Clinic at CHP are similar to other studies involving the SCD population in terms of racial background, distribution of SCD types, and insurance coverage.[232,236] As was previously discussed, the clinic's immunization records were largely lost after a move from paper to electronic records. Consequently, baseline documentation rates in this clinic's population may be lower than average. The effect of a similar QI in other clinics with higher baseline rates of vaccine documentation may not be as dramatic as was found in this assessment.

5.4.2 Public Health Relevance

As enabled through NBS, penicillin prophylaxis for infants with SCD significantly reduces their risk for potentially fatal pneumococcal infection. These initial services of diagnosis and immediate care often receive significant attention and resources in NBS. However, the public health program is intended to be comprehensive and span an individual's lifetime. This involves six primary components, which are education, screening, follow-up, diagnosis, treatment and management, and evaluation of programs for continuous quality improvement.[167,168]

In the NBS program, follow-up is comprised of both short-term and, in some states long-term, services. The latter begins once an infant has received a definitive diagnosis through the program and the necessary disease management or treatment has been initiated.[86] Services should be provided into adulthood in order to maximize the benefit of diagnosis through the program.[85] In the case of SCD, long-term health care includes complete pneumococcal vaccination as well as

cessation of penicillin after the age of five years old, when it has no longer been shown to provide significant benefit.[19,226] As this assessment demonstrates the effectiveness of a QI in increasing pneumococcal vaccination rates and discontinuing inappropriate penicillin prescription in children with SCD, it adds to current knowledge about how to successfully implement NBS services in the SCD patient population.

In 2008, a statement was put forth by the SACHDNC, an organization that was created to guide the US Department of Health and Human Services Secretary on NBS tests, policies, and guidelines. The statement came in response to studies which found that long-term follow-up in NBS is variably and inconsistently applied.[84,240,241] To clarify the role of this core service in NBS programs, the SACHNDNC specified that long-term follow-up should include "the assurance and provision of quality chronic disease management, condition-specific treatment, and age-appropriate preventative care throughout the lifespan of individuals identified with a condition included in newborn screening."[85] Additionally, it should ensure care coordination and "continuous quality improvement," as well as "active surveillance and evaluation of data related to care and outcomes." The project described by this assessment was carried out at a specialty sickle cell clinic to provide such services to children identified to have SCD through the NBS program.

First, this project demonstrates the value of the EHR to a pediatric sickle cell clinic's ability to coordinate their patients' care. The Sickle Cell Clinic of CHP is contracted with the Department of Health of the Commonwealth of Pennsylvania to follow-up on newborns identified with SCD through NBS in Western Pennsylvania and seeks to ensure their comprehensive, multidisciplinary care until their transition into adult care. This is in line with the intent of the NBS program to provide such care to individuals diagnosed through the program through the provision of both

primary care and specialty health care services.[242,243] The EHR is an invaluable tool for the care coordination that is necessary for this service, as it facilitates communication by providers across different clinics and health care systems.[234,238,244] This QI leveraged concerted efforts in collecting and updating the vaccination records of the clinic's pediatric SCD population, as well modifications to the EHR, to better enable this communication, thereby allowing for deficient pneumococcal vaccination status to be identified and provided by the specialty clinic or the child's pediatrician. This resulted not only in increased pneumococcal vaccination rates, but a decrease in inappropriate penicillin prescription. Finally, the QI promoted conversations between the family and the clinicians about discontinuing penicillin if indicated. This is consistent with another goal of a medical home, which is to engage in family-centered and culturally effective care.[126,242]

As it is another component of NBS, quality improvement was the primary focus of this assessment.[85] Quality improvement in NBS can be enabled by data-systems such as the EHR, which capture clinical care data that can be analyzed in order to inform clinical decisions and policies. This assessment engaged in record collection from the EHR in order to identify deficient vaccination documentation as a significant barrier to the age-appropriate cessation of penicillin for children with SCD. The data review also demonstrated that the interventions engaged in by the QI served as an effective means of addressing this barrier.

Finally, the importance of this assessment, which presents a strategy for discontinuing penicillin, is further emphasized by evidence that excessive antibiotic use may contribute to the emergence of resistant pneumococcal strains.[227] Increased resistance diminishes the effectiveness of prophylaxis in the SCD population.[226] As a primary intention of the NBS program for SCD is to reduce morbidity and mortality due to IPD, responsible implementation of this public health program calls for stopping penicillin when it is no longer recommended.[245]

While more evidence is needed, a number of additional populations, such as those with less severe SCD types and those who have received a surgical splenectomy, have been explored in the literature review as potential recipients of excess penicillin prescription. The findings of this assessment suggest that adoption of similar strategies by other SCD clinics may allow for more judicious use of penicillin. Ultimately, greater utilization of similar interventions may minimize the unintended, and likely deleterious, consequences of excessive penicillin prophylaxis in high-risk, immune-compromised populations.

5.5 CONCLUSION

In the 18-month time span evaluated by this assessment, all three metrics of improvement that the QI sought to improve, pneumococcal vaccine documentation, immunization rates, and appropriate penicillin prescription, were found to increase from baseline rates. Significant increases in vaccination documentation status, as well as appropriate penicillin prescription were found in the time period immediately following implementation of the QI. These changes were sustained or increased in the time periods that followed. While vaccination rates did not appear to significantly increase immediately after the intervention, complete vaccination rates were found to have significantly increased, by approximately 20%, by the final time period. This is consistent with improvements in vaccination rates that have demonstrated by other interventions that utilize the EHR in an urban, pediatric population.[234,236–238] Baseline pneumococcal vaccination rates that were consistent with, or even lower, than other literature focusing on the SCD population indicate a need to implement such interventions in high-risk population.[232] The importance of protection against pneumococcal infection and its connection to resistant strains further fuels this QI's

ultimate goal, which was to address excessive penicillin prescription. To further contribute with this effort, additional research is needed to more fully explore the barriers to pneumococcal vaccination and penicillin discontinuation, so that possible interventions may be implemented to address these concerns in the SCD population.

Appendix A IRB APPROVAL LETTER

University of Pittsburgh
Institutional Review Board

3500 Fifth Avenue
Pittsburgh, PA 15213
(412) 383-1480
(412) 383-1508 (fax)
http://www.irb.pitt.edu

Memorandum

To: Cheryl Hillery , MD
From: IRB Office
Date: 10/1/2018
IRB#: PRO18060433
Subject: Assessment of Hemoglobin Trait Notification in Western Pennsylvania Newborn Screening

---

The University of Pittsburgh Institutional Review Board reviewed and approved the above referenced study by the expedited review procedure authorized under 45 CFR 46.110 and 21 CFR 56.110. Your research study was approved under:

45 CFR 46.110.(7)

The IRB has approved the waiver for the requirement to obtain a written informed consent all procedures.

The risk level designation is Minimal Risk.

Approval Date: 10/1/2018
Expiration Date: 9/30/2019

For studies being conducted in UPMC facilities, no clinical activities can be undertaken by investigators until they have received approval from the UPMC Fiscal Review Office.

Please note that it is the investigator's responsibility to report to the IRB any unanticipated problems involving risks to subjects or others [see 45 CFR 46.103(b)(5) and 21 CFR 56.108(b)]. Refer to the IRB Policy and Procedure Manual regarding the reporting requirements for unanticipated problems which include, but are not limited to, adverse events. If you have any questions about this process, please contact the Adverse Events Coordinator at 412-383-1480.

The protocol and consent forms, along with a brief progress report must be resubmitted at least one month prior to the renewal date noted above as required by FWA00006790 (University of Pittsburgh), FWA00006735 (University of Pittsburgh Medical Center), FWA00000600 (Children's Hospital of Pittsburgh), FWA00003567 (Magee-Womens Health Corporation), FWA00003338 (University of Pittsburgh Medical Center Cancer Institute).

Please be advised that your research study may be audited periodically by the University of Pittsburgh Research Conduct and Compliance Office.

Appendix B TRAIT NOTIFICATION NEWBORN SCREENING LETTERS

B.1 Sickle S Trait Letter

04/21/2017

Ms. Jane Doe
100 Test St.
Pittsburgh, PA 15235

RE: Baby Male Doe
DOB: 03/01/2017

Dear Ms. Doe:

When your child was born, blood tests were done by the Commonwealth of Pennsylvania's newborn screening program. This letter is to let you know about your baby's blood test results.

Blood Screening Results:

- Your baby has **sickle S trait**.
- This means that each of the red blood cells contains normal hemoglobin and hemoglobin S.

Here are 5 things you should do:

1. Do NOT be alarmed. Do not worry.

- Sickle cell trait is NOT a disease and will not turn into the disease.

2. Think about getting both parents tested.

- If your child has sickle cell trait, that means that **at least one** parent carries the gene.
- **If both** parents carry the sickle cell gene, it means that you could have a baby with sickle cell disease in the future. This is something to think about.

3. Get more information:

- Read the pamphlet that comes with this letter.
- Call us at 412-692-3271 with any questions or concerns.
- Plan to come to a counseling session at Children's Hospital of Pittsburgh.

4. Share this letter with your baby's doctor.

5. Keep this letter in a safe place for your records and for your child.

Sincerely,

Cheryl A Hillery, MD
Director, Sickle Cell Program
Pediatric Hematology/Oncology

Debra Cohen, MD
Amma Owusu-Ansah, MD
Pediatric Hematology/Oncology

B.2 Hemoglobin C Trait Letter

04/21/2017

Ms. Jane Doe
100 Test St.
Pittsburgh, PA 15235

RE: Baby Male Doe
DOB: 03/01/2017

Dear Ms. Doe:

When your child was born, blood tests were done by the Commonwealth of Pennsylvania's newborn screening program. This letter is to let you know about your baby's blood test results.

Blood Screening Results:

- Your baby has **hemoglobin C trait**.
- This means that each of the red blood cells contains normal hemoglobin and hemoglobin C.

Here are 5 things you should do:

1. Do NOT be alarmed. Do not worry.

- Hemoglobin C trait is NOT a disease and will not turn into a disease.

2. Think about getting both parents tested.

- If your child has hemoglobin C trait, that means **at least one** carries the hemoglobin C gene.
- **If one parent carries the hemoglobin C gene, and one parent carries the sickle S gene,** then you could have a baby with sickle cell disease in the future. This is something to think about.

3. Get more information:

- Read the pamphlet that comes with this letter.
- Call us at 412-692-3271 with any questions or concerns.

4. Share this letter with your baby's doctor.

5. Keep this letter in a safe place for your records and for your child.

Sincerely,

Cheryl A Hillery, MD
Director, Sickle Cell Program
Pediatric Hematology/Oncology

Debra Cohen, MD
Amma Owusu-Ansah, MD
Pediatric Hematology/Oncology

Appendix C INFORMATION BROCHURE

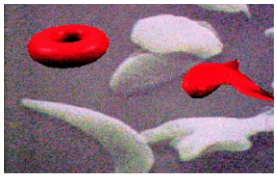
C.1 Sickle S Trait Brochure

What services are available in Western Pennsylvania for identifying persons with Hemoglobin S?

The doctors, nurses and other health care professionals at Children's Hospital of Pittsburgh of UPMC are available to answer your questions.

Children's Hospital of Pittsburgh | of UPMC

HEMOGLOBIN S TRAIT



Comprehensive Hemoglobinopathy Program
Blood and Marrow Transplantation Program
Division of Pediatric Hematology/Oncology

4401 Penn Avenue
Pittsburgh, PA 15224
Phone 412-692-6059

Physicians
Cheryl A. Hillery, MD
Debra E. Cohen, MD
Amma Owusu-Ansah, MD

Physician Assistants
Margaret Holtz, PA-C
Kelsey Platte, PA-C

Social Worker
Pamela Mwiinde, MSW

Behavioral Medicine
Janessa Nowlen, PsyD

CLMIT 09-030

Front

What is hemoglobin?

Hemoglobin (Hb) is the special protein within the red blood cell that carries oxygen from the lungs to the rest of the body.

Where does your hemoglobin come from?

Your hemoglobin type is inherited through family genes. The color of your hair, the color of your eyes, your body build and your hemoglobin type are all examples of things about you that are determined by genes. You receive one gene for hemoglobin type from your mother and one from your father.

Hemoglobin A or normal adult hemoglobin is the most common type. There are more than 500 different types or variations of hemoglobin.

What is hemoglobin S?

Hemoglobin S is often found in African Americans. It is common in people of African, Mediterranean, Middle Eastern and Indian origin.

Hemoglobin S behaves differently than normal hemoglobin A. Red cells with mostly hemoglobin S can become hard and sickle-shaped.

People with hemoglobin S trait inherit a normal hemoglobin gene (Hb A) from one parent and a hemoglobin S gene (Hb S) from the other parent.

This results in hemoglobin AS or hemoglobin S trait. A person with hemoglobin S trait may also be called a sickle cell carrier. Hemoglobin S trait is not a disease.

It will not turn into a disease. Hemoglobin S trait should cause no health problems and requires no special medical care.

Counseling regarding the trait is important, however, because the hemoglobin gene can be passed on to a carrier's child.

The most important aspect of identifying people with hemoglobin S trait is informing them of their risk of having a child with a serious disease.

What is Sickle Cell disease?

A type of sickle cell disease called sickle cell anemia occurs when a person inherits the hemoglobin S gene from each parent (Hb SS). The red cells contain only hemoglobin S and no normal hemoglobin A. A person with sickle cell disease has red cells that are sickle-shaped and block the body's small blood vessels. *(See Figure 1.)*

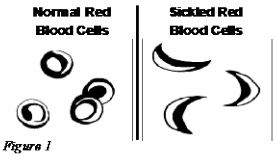


Figure 1

There are other hemoglobin types, such as hemoglobin C or hemoglobin E, that in combination with the gene for sickle hemoglobin can result in different forms of sickle cell disease (Hb SC, Hb SE, Hb S/beta thalassemia).

A child with sickle cell disease needs close medical attention from his or her own doctor and should also be followed by a Comprehensive Care Program offering specialized services for children with sickle cell disease. The child's caregivers should be educated about the disease and understand the child's special needs.

Patterns of Inheritance

If two people with hemoglobin S trait have a child, there is a 50 percent risk that the child will have hemoglobin S trait (hemoglobin AS). There is also a 25 percent chance the child will be unaffected (hemoglobin AA) and a 25 percent chance that the child will have Sickle cell disease (hemoglobin SS). These risks are true for each pregnancy. *(See Figure 2.)*

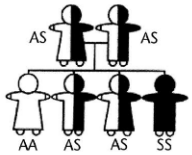


Figure 2

If one parent has hemoglobin S trait and the other has normal hemoglobin, it is unlikely that any of their children will have sickle cell disease. However, there is a 50% chance with each pregnancy that the child will have hemoglobin S trait (Hb AS). (*See Figure 3.*)

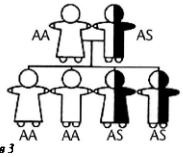


Figure 3

Back

C.2 Hemoglobin C Trait Brochure

If one parent has hemoglobin C trait and the other has normal hemoglobin, it is unlikely that any of their children will have hemoglobin C disease. However, there is a 50 percent chance with each pregnancy that the child will have hemoglobin C trait (Hb AC). *(See Figure 3)*

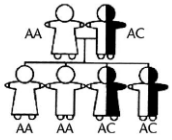


Figure 3

If one parent has sickle cell trait (Hb AS) and one parent has hemoglobin C trait (Hb AC) there is a 25 percent risk that the child will have sickle cell trait and a 25 percent risk that the child will have hemoglobin C trait. There is also a 25 percent chance the child will be unaffected (Hb AA) and a 25 percent chance that the child will have sickle cell disease (Hb SC). *(See Figure 4)* These risks are true for each pregnancy.

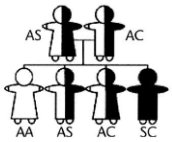


Figure 4

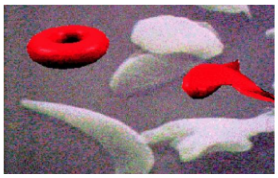
What services are available in Western Pennsylvania for identifying persons with Hemoglobin C?

Doctors, nurses and health care professionals at Children's Hospital of Pittsburgh of UPMC are available to answer your questions.

MCAER 0108-091

Children's Hospital of Pittsburgh of UPMC

HEMOGLOBIN C TRAIT



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Kelsey Platte, PA-C

Social Worker
Pamela Mwiinde, MSW

Behavioral Medicine
Janessa Nowlen, PsyD

Front

What is hemoglobin?

Hemoglobin (Hb) is the special protein within the red blood cell that carries oxygen from the lungs to the rest of the body.

Where does your hemoglobin come from?

Your hemoglobin type is inherited through family genes. The color of your hair, the color of your eyes, your body build and your hemoglobin type are all examples of things about you that are determined by genes. You receive one gene for hemoglobin type from your mother and one from your father.

Hemoglobin A or normal adult hemoglobin is the most common type. There are more than 500 different types or variations of hemoglobin.

What is hemoglobin C?

Hemoglobin C is a hemoglobin variant often found in West Africans and their descendants. In the United States, hemoglobin C occurs in 2 to 3 percent of the African American population.

What is hemoglobin C trait?

People with hemoglobin C trait inherit a normal hemoglobin gene (Hb A) from one parent and a hemoglobin C gene (Hb C) from the other parent.

This results in hemoglobin AC or hemoglobin C trait. A person with hemoglobin C trait may also be called a hemoglobin C carrier. Hemoglobin C trait is not a disease. It will not turn into a disease. Hemoglobin C trait should cause no health problems and requires no special medical care.

Counseling regarding the trait is important because the hemoglobin C gene can be passed on to a carrier's child.

The most important aspect of identifying people with hemoglobin C trait is informing them of their risk of having a child with a serious disease.

What is hemoglobin C disease?

Hemoglobin C disease occurs when a person inherits a hemoglobin C gene from each parent (Hb CC). The red cells contain only hemoglobin C and no normal hemoglobin A. Most people with hemoglobin C disease lead fairly healthy lives and live to a normal age. Possible symptoms include mild anemia (low red blood counts), slightly large spleen, and gallstones. Genetic counseling can help a family better understand hemoglobin C disease.

What is hemoglobin SC disease?

Persons with hemoglobin SC disease inherit a hemoglobin S (sickle) gene from one parent and a hemoglobin C gene from the other parent. Hemoglobin SC disease is a form of sickle cell disease. The person with hemoglobin SC disease has red cells in the shape of sickles. *(See Figure 1.)* The sickling of red cells may cause the following medical problems: anemia (low red blood counts), painful crises, enlarged spleen, infections, lung problems and strokes.

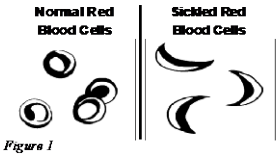

Figure 1

A child with hemoglobin SC disease needs close medical attention from his own doctor and should also be followed by a Comprehensive Care Program offering specialized services for children with sickle cell disease. The child's caregivers should be educated about the disease and understand the child's special needs.

Patterns of Inheritance

If two people with hemoglobin C trait have a child, there is a 50 percent risk that the child will have hemoglobin C trait (hemoglobin AC). There is also a 25 percent chance the child will be unaffected (hemoglobin AA) and a 25 percent chance that the child will have hemoglobin C disease (hemoglobin CC). *(See Figure 2.)* These risks are true for each pregnancy.

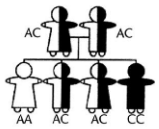

Figure 2

Back

Appendix D WAIVER OF INFORMED CONSENT

Comprehensive Hemoglobinopathy Program
4401 Penn Avenue
Pittsburgh PA 15224-1334
Phone (research): 412-692- 6467
Phone (clinical): 412-692-7580

UPMC | CHILDREN'S HOSPITAL OF PITTSBURGH

Research Study Consent:
Hemoglobinopathy Trait Notification in Western Pennsylvania Newborn Screening

Dear Ms. [NAME],

You are being invited to participate in a research study because you were notified by letter this past year about your baby's hemoglobin trait that was identified by the Pennsylvania Newborn Screen program. The purpose of this study is to better understand the experience of parents who receive this notification letter.

Participation in this research study involves a brief (approximately 10 minutes) survey. The survey asks about general understanding of sickle cell trait, how you felt after reading the letter, and who you may have shared the letter's information with. For your reference, a copy of the notification letter and information brochure provided in the original mailing are again included with this survey. **You should only participate in this study if you are 18 years of age or older. Survey responses are voluntary.**

While there is a potential risk of breach of confidentiality by participating in this study, we are taking all reasonable measures to ensure that your answers and participation in this study will remain as confidential (private) as possible. Your answers will be recorded in a way that does not connect them with your identity. All paper records related to your involvement in this research study will be stored in a locked container and eventually destroyed after completion of the research project. Authorized representatives from the University of Pittsburgh Research Conduct and Compliance Office may review your data solely for the purpose of monitoring the conduct of this study. **You will not be identified by name in any publication of the research results. There is also a risk that some of the questions in this survey may make you uncomfortable. You can choose to not answer any question in this survey. There are no direct benefits to you by participating in this study. However, we hope to use this information to improve our communication with future parents.**

If you agree to participate, please mail the paper survey back to Children's Hospital of Pittsburgh Pediatric Sickle Cell Program in the enclosed, pre-paid envelope. If you decide that you no longer wish to participate after returning the survey, please let us know and we will remove and destroy your responses from the study. If we have not received your survey within one month, we may contact you by phone to complete the survey. You can decline to participate at that time.

This study is being conducted as part of the thesis requirement for Caitlin Russell's Master's Degree in Genetic Counseling at University of Pittsburgh. The Primary Investigator of this study, Cheryl Hillery, MD, is the Director of the Sickle Cell Program in the Department of Pediatrics at UPMC-Children's Hospital of Pittsburgh. She is responsible for sending out the notification letters for hemoglobin traits identified via Newborn screening in the Western Pennsylvania region (Region 6).

The risks of participating in this study are minimal. There is a potential risk of a breach of confidentiality by participating in this study. However, your survey responses will be kept confidential and all reasonable measures will be taken to ensure confidentiality of your answers and your participation in this study. Authorized representatives from the University of Pittsburgh Research Conduct and Compliance Office may review your data solely for the purpose of monitoring the conduct of this study. There is also a chance that you find a question I ask during the survey upsetting or uncomfortable. If you choose to participate in this survey and there is a question I ask that you do not wish to answer for this or any other reason, you can just tell me. We will skip that question. You can also tell me at any time that you no longer wish to participate in the survey. If you decide that you no longer wish to participate after the call has ended, please let us know and we will remove and destroy your responses from the study.

Lastly, there are no direct benefits to you by participating in this study. If you have any questions or concerns about this study, you may contact Angela Martino, RN, Research Nurse Coordinator, at 412-692-6467. If you wish to speak with someone about the health information discussed in the letter, you may contact the Sickle Cell Program at 412-692-3271. If you have any questions about your rights as a research subject, please contact the Human Subjects Protection Advocate at the University of Pittsburgh IRB Office, at 866-212-2668.

- Do you have any questions before we begin? **[Q4]** Do I have your permission to begin the survey?

If no to Q4:

- Thank you, that is not a problem. I very much appreciate your time today. Have a good day.

If yes to Q4:

Thank you. I appreciate your time allowing me to continue. *Continue with survey*

Survey Script

See Survey Scripts attached in Section 2.8

Appendix E MAIL SURVEY

UPMC | CHILDREN'S HOSPITAL OF PITTSBURGH

Comprehensive Hemoglobinopathy Program
4401 Penn Avenue
Pi#sburgh PA 15224-1334
Phone (research): 412-692-6467
Phone (clinical): 412-692-7580

Sickle S Trait Notification Letter Survey

Thank you for your willingness to participate in this research study related to notification of your baby's Sickle S trait. A copy of the letter and the information brochure is included for your reference. We hope this survey will improve how future parents learn about their baby's trait status.

Please answer the questions below to the best of your ability. You can skip any question you do not wish to answer. This survey has 4 parts and should take about 10 minutes to complete. Your responses to this survey will be kept confidential. If you have questions about this study, please contact Study Coordinator, Angela Martino, BSN, RN at 412-692-6467. If you would like to speak to someone about the health information in the letter, please contact the Pediatric Sickle Program at Children's Hospital of Pittsburgh at 412-692-3271.

I have read the cover letter, am over 18 years old, and agree to participate *(check here)*: ☐

PART 1: What did you learn from the letter? *Please select one box per question*

1. Did the letter make it clear that there is a difference between sickle cell trait and sickle cell disease? *(This is not a question that can be answered correctly or incorrectly)*

   ☐ **Yes** ☐ **No** ☐ **Unsure**

2. **Can a child with sickle cell trait ever develop sickle cell disease?**

   ☐ **Yes** ☐ **No** ☐ **Unsure**

3. **Do both parents have to have sickle cell trait for a baby to be born with sickle cell disease?**

   ☐ **Yes** ☐ **No** ☐ **Unsure**

4. **If one parent has sickle S trait and one parent has hemoglobin C trait, could they have a baby with disease?**

   ☐ **Yes** ☐ **No** ☐ **Unsure**

5. **If you have sickle cell trait, could your brother or sister also have sickle cell trait?**

   ☐ **Yes** ☐ **No** ☐ **Unsure**

6. **Can you choose which genes are passed onto your children?**

   ☐ **Yes** ☐ **No** ☐ **Unsure**

7. **Can you "catch" sickle cell disease like a cold?**

   ☐ **Yes** ☐ **No** ☐ **Unsure**

8. **If both parents have sickle cell trait, what is the chance that their child has sickle cell disease?**

   ☐ **0%** ☐ **25%** ☐ **50%** ☐ **100%** ☐ **Unsure**

Survey Front

PART 2: How did the letter make you feel?
Please respond to each statement by marking one box per row

Since receiving the trait notification letter…	Never	Rarely	Sometimes	Often	Always
I felt fearful about my baby having Sickle S trait	☐	☐	☐	☐	☐
I found it hard to focus on anything other than my anxiety about my baby having Sickle S trait	☐	☐	☐	☐	☐
My worries about my baby having Sickle S trait overwhelmed me	☐	☐	☐	☐	☐
I felt uneasy about my baby having Sickle S trait	☐	☐	☐	☐	☐
I felt nervous about my baby having Sickle S trait	☐	☐	☐	☐	☐
I felt like I needed help for my anxiety about my baby having Sickle S trait	☐	☐	☐	☐	☐
I felt anxious about my baby having Sickle S trait	☐	☐	☐	☐	☐
I felt tense about my baby having Sickle S trait	☐	☐	☐	☐	☐

PART 3: Who do you plan on sharing the letter's information with?
Please select one box per statement about those individuals who you have talked with or plan to talk with about the letter's information

I feel comfortable talking about sickle cell trait/disease with my partner

☐ **Yes** ☐ **No** ☐ **Unsure**

I have already shared/plan to share my baby's trait status with my baby's doctor

☐ **Yes** ☐ **No** ☐ **Unsure**

I have already shared/plan to share my baby's trait status with my own doctor

☐ **Yes** ☐ **No** ☐ **Unsure**

I plan on sharing my baby's trait status with him/her when he/she is older

☐ **Yes** ☐ **No** ☐ **Unsure**

PART 4: Please include any additional thoughts or feelings about the notification letter that you would like us to know:

Survey Back

The survey sent for HbC trait screening results was identical except "Sickle S trait" was replaced with "Hemoglobin C trait."

Appendix F TELEPHONE SURVEY SCRIPT

Phone Survey Informed Consent Script

Hello, my name is Caitlin Russell. I am a Masters student in the genetic counseling program at the University of Pittsburgh. I am calling regarding a research study I am conducting for my Masters thesis. Would I please be able to speak with the parents or guardians of [NAME]?

I am calling to follow up on a survey that was mailed to you approximately [NUMBER] months ago. It was about the letter your received shortly after your baby's birth regarding his/her hemoglobinopathy trait that was identified during Pennsylvania's Newborn Screening program. **Are you 18 years or older?** (*if yes, continue).* **[Question 1] Do you recall receiving this survey?**

If yes to Question 1:
- **[Question 2] Did you already complete and return the survey?**

If yes to Q2:
- Thank you. Do you have any further questions or concerns?

If no to Q2:
- *Continue to "If no to Q1 or Q2"*

If no to Q1 OR Q2:
- Would you be interested in hearing more about this study? *(If no, thank them and end call; if yes:)* For my Master's thesis, I am conducting a research study about the experience of parents who receive the Sickle Cell Newborn Screening letter. **[Q3] Do you recall receiving this letter? It would have been sent about 2 weeks after your baby was born.**

If no to Q3:
- *End call:* That is not a problem. Thank you so much. I very much appreciate your time today and hope you have a good day.

If yes to Q3:
- I am calling to see if you are interested in participating in a research study about that letter. Your participation would involve completing a short survey on the phone. It should take about 10 minutes. The survey asks about general understanding of sickle cell trait, how you felt after reading the letter, and who you may have shared the letter's information with.

  Your participation is completely voluntary. This means that you do not have to participate in this study unless you want to. This call is not being recorded. Your decision whether or not to participate will not affect your relationship with your or your child's doctors or with any other health care providers.

The risks of participating in this study are minimal. There is a potential risk of a breach of confidentiality by participating in this study. However, your survey responses will be kept confidential and all reasonable measures will be taken to ensure confidentiality of your answers and your participation in this study. Authorized representatives from the University of Pittsburgh Research Conduct and Compliance Office may review your data solely for the purpose of monitoring the conduct of this study. There is also a chance that you find a question I ask during the survey upsetting or uncomfortable. If you choose to participate in this survey and there is a question I ask that you do not wish to answer for this or any other reason, you can just tell me. We will skip that question. You can also tell me at any time that you no longer wish to participate in the survey. If you decide that you no longer wish to participate after the call has ended, please let us know and we will remove and destroy your responses from the study.

Lastly, there are no direct benefits to you by participating in this study. If you have any questions or concerns about this study, you may contact Angela Martino, RN, Research Nurse Coordinator, at 412-692-6467. If you wish to speak with someone about the health information discussed in the letter, you may contact the Sickle Cell Program at 412-692-3271. If you have any questions about your rights as a research subject, please contact the Human Subjects Protection Advocate at the University of Pittsburgh IRB Office, at 866-212-2668.

- Do you have any questions before we begin? **[Q4]** Do I have your permission to begin the survey?

If no to Q4:

- Thank you, that is not a problem. I very much appreciate your time today. Have a good day.

If yes to Q4:

Thank you. I appreciate your time allowing me to continue. *Continue with survey*

Survey Script

See Survey Scripts attached in Section 2.8

Appendix G PROMIS SCORING TABLE

Anxiety 8a - Adult v1.0		
Short Form Conversion Table		
Raw Score	T-score	SE*
8	37. 1	5.5
9	43.2	3.3
10	45.9	2.8
11	47.8	2.5
12	49.4	2.3
13	50.8	2.2
14	52.1	2.1
15	53.2	2.0
16	54.3	2.0
17	55.4	2.0
18	56.4	2.0
19	57.4	2.0
20	58.4	2.0
21	59.4	2.0
22	60.4	2.0
23	61.4	2.0
24	62.5	2.0
25	63.5	2.0
26	64.5	2.0
27	65.6	2.0
28	66.6	2.0
29	67.7	2.0
30	68.7	2.0
31	69.8	2.0
32	70.8	2.0
33	71.9	2.0
34	73.0	2.0
35	74.1	2.0
36	75.4	2.0
37	76.7	2.1
38	78.2	2.3
39	80.0	2.6
40	83.1	3.4

SE* = Standard Error on T-Score

Appendix H MAIL AND TELEPHONE SURVEY RESPONSES

H.1 Knowledge Questionnaire

Question *(Answer)*		Percent Correct	Percent Incorrect	Percent Unsure
1. Did the video make it clear that there is a difference between sickle cell trait and sickle cell disease? This is not a question that can be answered correctly or incorrectly *(Yes)*	Mail	100%	0%	0%
	Telephone	91.4%	6.1%	2.5%
	Total	**95.2%**	5.3%	2.1%
2. Can a child with sickle cell trait ever develop sickle cell disease? *(No)*	Mail	76.9%	7.7%	16.1%
	Telephone	70.4%	16.1%	13.6%
	Total	**71.3%**	14.9%	13.8%
3. Do both parents have to have sickle cell trait for a baby to be born with sickle cell disease *(Yes)*	Mail	53.9%	38.5%	7.7%
	Telephone	65.4%	33.3%	1.2%
	Total	**63.8%**	34.0%	2.1%
4. If one parent has sickle S trait and one parent has hemoglobin C trait, could they have a baby with disease? *(Yes)*	Mail	61.5%	15.4%	23.1%
	Telephone	51.9%	21.0%	27.2%
	Total	**53.2%**	20.2%	26.6%
5. If you have sickle cell trait, could your brother or sister also have sickle cell trait? *(Yes)*	Mail	69.2%	23.08%	7.7%
	Telephone	75.3%	21.0%	3.7%
	Total	**74.5%**	21.3%	4.3%

6. Can you choose which genes are passed onto your children? *(No)*	Mail	100%	0%	0%
	Telephone	92.6%	2.5%	4.9%
	Total	**93.6%**	2.1%	4.3%
7. Can you "catch" sickle cell disease like a cold? *(No)*	Mail	100%	0%	0%
	Telephone	100%	0%	0%
	Total	**100%**	0%	0%

Mail: n = 13; Telephone: n = 81; Total: n = 94

H.2 Sharing

Have you or do you plan on sharing the letter's information with your:	**Method**	**Yes**	**No**	**Unsure**
Partner	Mail	100%	0%	0%
	Telephone	96.3%	3.7%	0%
	Total	**96.8%**	3.2%	0%
Child	Mail	100%	0%	0%
	Telephone	98.8%	0%	1.2%
	Total	**98.9%**	0%	1.1%
Child's Doctor	Mail	100%	0%	0%
	Telephone	88.8%	7.4%	3.7%
	Total	**90.4%**	6.4%	3.2%
Own Doctor	Mail	76.9%	15.4%	7.7%
	Telephone	70.4%	27.2%	2.5%
	Total	**71.3%**	25.5%	3.2%

Mail: n = 13; Telephone: n = 81; Total: n = 94

Appendix I SELECTED MAIL AND TELEPHONE RESPONSES

Mail:

I checked sometimes in those 3 boxes because that is how I felt when I first found out she had the trait. But now that I learned about it and read about it I feel much better

The letter made me feel generally uncertain…about the present and the future. I could tell it was intended as notification and tried to reassure me that nothing is wrong, but it is still very intimidating to be contacted by the Hematology/Oncology department of Children's Hospital...

My husband is Hispanic and we know I do not carry the Hemoglobin S trait; how do we go about getting him and members of this family tested for the Hemoglobin S trait? His country never tested for this.

Telephone:

I read it over and over. I was glad they put that number on there. I was very worried.

Doctor called and told me to take him in immediately, that his "hemoglobin levels are low."

My husband has it and he knows biology and was able to explain it to me.

I have three children with it [hemoglobin c trait]. It's not a big deal.

I was bawling my eyes out for the first ten minutes. I was confused about it [trait] and the disease, that it is not the disease. Also, the timing with all the hormones.

Everyone in my family has sickle cell.

It did scare me when I saw that letter. What's going on? Then I read it and was reassured, that it's something to think about when she is finding her life partner and having babies.

Appendix J QUALITY INITIATIVE REVIEW COMMITTEE APPROVAL LETTER

Project Sponsor,

The Quality Improvement Review Committee is pleased to inform you that your QI project has been approved.

We have also notified your local quality department of this approval and encourage you to share updates on the project's progress.

Please note that results of QI projects must be reviewed by local quality directors and approved by the Chief Quality Officer prior to dissemination (via presentation or publication) outside of UPMC. UPMC has adopted the Standards for Quality Improvement Reporting Excellence guidelines, SQUIRE 2.0 as the suggested reporting format.

For multi-center projects, the QRC **approval** refers only to that **part of the project being performed at UPMC facilities** and the sponsors are responsible for obtaining approval from other non UPMC facilities participating in the project.

We suggest that you share your findings on this project with the QRC. When your project is complete, please navigate to the Quality Improvement Project Portal and go to "My Projects." Select the project and go to the "Project Summary" tab, add the findings in the "Project Results" field, and click "Submit Project Results to QRC."

Projects reviewed and approved by the UPMC Quality Improvement Review Committee do not meet the federal definition of research according to 45 CFR 46.102(d) and do not require additional IRB oversight.

Project Submission Details:

Project ID: 1528

Project Title: Optimization of pneumococcal immunizations and appropriate penicillin prophylaxis at UPMC Children's Hospital of Pittsburgh pediatric sickle cell clinic

Project Sponsor:

Cheryl Hillery ** Faculty - Research, Physician ** UPP18 PEDS Hematology_Oncology

Project Co-Sponsor(s):

Suzanne Komaniak ** RN Coordinator ** CHP-Hematology Oncology Admin

Margaret Holtz ** Physician Assistant, Staff ** UPP18 PEDS Hematology_Oncology

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Submitted By:

Cheryl Hillery ** Faculty - Research, Physician ** UPP18 PEDS Hematology_Oncology

Additional Information from the QRC:

To view the full project, log in to the Quality Improvement Project Portal, click on "My QI Projects," and select project.

Thank you for submitting your project for our review

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