EVALUATION OF A COMMUNITY-BASED ORGANIZATION'S TRANSITION PROGRAM FOR SICKLE CELL DISEASE AND ITS EFFECT ON ADOLESCENTS' AND YOUNG ADULTS' TRANSITION READINESS

by

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ABSTRACT

Background: The need for transition care for adolescent and young adults (AYA) with sickle cell disease (SCD) has become evident in recent years, as AYA with SCD are living longer lives due to the successful implementation of preventative treatment measures. This study seeks to evaluate the current SCD transition program of a community-based organization (CBO) in Pittsburgh, as well as to conduct interviews with CBO staff/volunteers and health care professionals in order to assess the current state of the program and any barriers that are present to the transition process.

Methods: AYA completed two self-administered surveys, one regarding their experience with the CBO's transition program, and one assessing their transition readiness. Interviews were conducted with CBO staff/volunteers and health care professionals, which were analyzed using thematic analysis.

Results: No statistically significant change in readiness was observed in the AYA study population before and after participation in the CBO transition program. Interviews revealed five main themes: Parental Encouragement of Autonomy, Negative Feelings of AYA Affecting Transition, Presentation of Transition to AYA, Variability Regarding AYA Readiness to Transition, and Logistical Barriers to Transition.

Conclusions: AYA readiness did not significantly change based on the transition program. This study was the first to evaluate a CBO's transition program. The results of the surveys and interviews can help inform CBO staff/volunteers as well as health care professionals about the needs

of the local AYA population regarding transition. This can also allow suggested changes to be implemented and any identified barriers to be addressed.

Public Health Significance: This study is designed to impact public health by assessing the current transition program in Pittsburgh and suggesting policy changes in order to help improve the process of transition for AYA with SCD in the community.

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1.0   INTRODUCTION

Sickle cell disease (SCD) is a chronic, lifelong illness characterized by abnormal hemoglobin that can cause sickling of the red blood cells. The signs and symptoms of SCD typically first appear during childhood and can include anemia, pain crises, organ damage, and recurrent infections.[1] Survival into adulthood has improved drastically since the 1970s.[2] The median survival for HbSS disease was around 20 years in the 1970s[3] and is currently around 42-48 years.[4] This increased survival to adulthood is believed to be due in part to the introduction of newborn screening for early detection and education, prophylactic penicillin, and effective vaccinations.[5] Other contributing factors include more timely medical interventions, more preventive measures and improved drug therapy.[5]

As a result of prolonged survival, there is an increased need for adult care providers, as well as education for adolescents who must leave their pediatric providers and transition to an adult care team. In this context we can define transition as "the process of changing from a pediatric to an adult model of health care."[6] These transitions are often dictated by biological age, not an individual's independence or readiness for transition.[7] A variety of factors including type and severity of SCD, health complications from SCD, an understanding of one's health condition, independence, and education level can all impede or promote a successful transition.[7]

Poor transition has been associated with negative outcomes, including increased morbidity and mortality in individuals with SCD over the age of 18.[8] This also has implications for health

care costs, as a failed transition can present as missed follow-up appointments in the adult care facility, as well as increased emergency department visits and re-hospitalizations.[8] Additionally, after undergoing transition, some individuals return to their pediatric care provider suggesting poor satisfaction with the adult provider.[8] This is all evidence for the importance of a successful transition process.

In Pittsburgh, The Children's Sickle Cell Foundation, Inc. (CSCF), a local community-based organization, in conjunction with the Pediatric Sickle Cell Clinic at the Children's Hospital of Pittsburgh of UPMC (CHP) and the UPMC Adult Sickle Cell Program, works to help adolescents and young adults (AYA) with SCD in Pittsburgh make the transition to the UPMC Adult Sickle Cell Program.

This project lends a unique perspective to the transition process for AYA with SCD. The literature is lacking a description of a successful transition model from a community-based sickle cell organization. By providing an overview of CSCF's transition program, other community-based organizations could learn from this transition model in order to help establish partnerships with medical centers or their own community-based transition programs. This project also brings awareness to the need for a quality transition program for AYA with SCD. The study evaluated the AYA's readiness to transition and elicited their experiences with the program. The goal of the study is to use information from AYA's experiences and suggestions for improvement to modify the existing transition program.

1.1 SPECIFIC AIMS

1.1.1 Specific Aim 1

To describe a community-based organization's (CBO) transition program.

1.1.2 Specific Aim 2

To assess AYA's readiness to transition and to determine if AYA transition readiness improves following participation in the CBO's transition program.

1.1.3 Specific Aim 3

To assess AYA's experiences with the CBO's transition program and following transition to the adult medical program.

1.1.4 Specific Aim 4

To elicit perspectives and experiences regarding transition from 1) CBO staff and volunteers, 2) the pediatric clinical team and 3) the adult clinical team.

2.0   LITERATURE REVIEW

2.1 OVERVIEW OF SICKLE CELL DISEASE

The term "sickle cell disease" (SCD) refers to a group of hereditary blood disorders, called hemoglobinopathies. These disorders affect the way that the body produces hemoglobin. In SCD, the red blood cells (RBCs) can become crescent or sickle shaped. Because sickle hemoglobin can adhere to itself after delivering oxygen to tissues, long chains may be formed that can eventually cause the RBCs to become irregularly shaped into the aforementioned sickle or crescent shape.[9] These irregularly shaped RBCs can occlude (or obstruct) blood vessels and block blood flow, which is call "vaso-occlusion". Sickle RBCs also have a shorter lifespan than their normal disk-shaped counterparts. This decreased lifespan and intermittent stoppage of blood flow causes most of the primary symptoms of SCD, including pain crises, hemolytic anemia, and organ damage.[10]

SCD is estimated to affect 72,000 to 98,000 individuals in the United States.[11] In the US, SCD is most common in the African American population, with an estimated incidence rate of 1 in 365.[11] SCD can appear in any racial group, but appears more commonly in individuals from Central and South America, Africa, and people of Asian, Indian, Middle Eastern, or Mediterranean descent.[12] It is estimated that approximately 300,000 newborns are born with SCD worldwide each year.[13] SCD is also the most common genetic condition that is caused by a single gene mutation.[14]

Worldwide, Hemoglobin SS disease (HbSS) accounts for approximately 64% of all hemoglobinopathies.[14] Other variants of SCD include HbSC (16.1%) and HbS/beta thalassemia (3.5%).[13,14]

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2.1.1 Molecular Genetics of SCD

Hemoglobin is made up of four polypeptide subunits. Initially, hemoglobin is made up of two alpha globin chains and two gamma globin chains. The two gamma globin chains are eventually replaced by beta chains at around 6 months of age.[15] This process transforms the fetal hemoglobin (HbF) into adult hemoglobin (HbA).

At the molecular level, abnormal hemoglobin, or hemoglobin S (HbS) is caused by an A to T point mutation in the *HBB* gene, which codes for β-globin chains that make up a subunit of hemoglobin. The end result of this mutation is the production of a protein with a valine in place of glutamic acid in the 6th amino acid (Glu6Val), which causes HbS to be produced.[16] HbS causes the hemoglobin inside RBCs to crystalize and become less soluble when oxygen has been released from the hemoglobin molecule; this causes the RBCs to polymerize, which can make them sickle-shaped, increasing the risk for vascular obstruction.

Individuals with SCD typically have a Glu6Val point mutation in *HBB*, as well as a second deleterious mutation. The most common type of SCD, HbSS disease, results from two homozygous mutations for the Glu6Val variant. Other possible combinations of variants include one HbS mutation (Glu6Val), in combination with a different mutation such as HbC (Glu6Lys), HbD-Punjab (Glu121Gln), HbE (Glu26Lys), HbO-Arab (Glu121Lys), or a beta thalassemia pathogenic variant in the same gene on the opposite chromosome.[17]

Beta thalassemia occurs when the β-globin chains are reduced or completely absent due to mutations in the *HBB* gene. They can be co-inherited with HbS, which results in sickle cell-beta thalessemias. While the previously mentioned pathogenic mutations are the more common causes of SCD or sickle cell-beta thalassemia, there are other pathogenic mutations in *HBB*. Many of

these mutations can cause hemoglobinopathies that are unrelated to SCD. To date, ClinVar has catalogued over 200 pathogenic mutations in this gene.[18]

Sickle cell-beta thalessemias are typically classified into one of two categories: HbS/β^0-Thalassemia (HbS/β^0-Thal) and HbS/β^+-Thalassemia (HbS/β^+-Thal). The genotype HbS/β^0-Thal has a mutation in *HBB* that prevents HbA from being produced at all.[19] Because of the absence of HbA, HbS/β^0-Thal often has similar severe clinical manifestations to HbSS disease.[19] These two can be distinguished based on the characteristics of the RBCs, the results of the hemoglobin electrophoresis or high-performance liquid chromatography (HPLC), and/or the genotype.[20] HbSS RBCs will be normocytic and some of the RBCs will be sickle shaped, while HbS/β^0-Thal will have microcytic RBCs with targets also present and possibly fewer sickle shaped cells.[20] In HbS/β^+-Thal, some HbA is produced. HbA levels for individuals with HbS/β^+-Thal can range from less than 5% to up to 45%, with higher levels of HbA typically being associated with a milder phenotype.[19] Clinical features of sickle cell-beta thalessemias include anemia as well as the features of sickle cell disease.[19] Sickle cell-beta thalessemias are categorized as a type of SCD, along with HbSS, HbSC, HbE, HbD, HbO, and other variants of SCD.[19] HbSS disease is also referred to as sickle cell anemia (SCA).[8]

2.1.2   History of SCD

In 1910, Dr. James Herrick published the first documented case of SCD in the Western world.[21] In this publication, Herrick reported a "large number of thin, elongated sickle-shaped and crescent-shaped forms [of red blood cells]."[21] At the end of his case study, Herrick concluded that no diagnoses could be made from the signs and symptoms presented by the patient, but posited possible explanations, including an intestinal parasite or syphilis.[21] Shortly after Herrick's case

report was published, Benjamin Earle Washburn, a fourth-year medical student in Charlottesville, Virginia, published the second documented case of SCD.[22]

By the 1920s, enough evidence had been gathered to determine the inheritance pattern of sickle cell anemia (SCA), also known as HbSS disease.[23] In 1923, W.H. Taliaferro and J.G. Huck published a paper describing the extent of SCA in a family in Virginia.[23] After delineating the inheritance of N (normal red blood cells) and S (sickle cells) within the family, Taliaferro and Huck concluded that SCA is an inherited condition that acts as a single Mendelian trait.[23]

Despite the growing literature being published on SCA at this time, there was still debate regarding its etiology. In the early 1920s, there was a general belief that if an individual had a positive sickle cell blood test, then he/she could transition from one severity of disease (symptomless, mild, or severe) to another (and back) throughout his/her lifetime.[24,25] It was not until 1949 that the difference between SCA and sickle cell trait was clearly outlined.[26,27]

In 1926, Cooley and Lee suggested the name "sickle cell anemia" for individuals with hemolytic anemia, and the term "sicklemia" for individuals who had in vitro sickling, but otherwise no significant health concerns related to this sickling.[28] Several decades went by before Linus Pauling et al[29] described SCA as the first molecular disease, meaning that this was the first occasion in which a disease was associated with a change in protein structure. Using electrophoresis, the Pauling research team determined that HbS differed in structure from HbA.[29] Seven years later another important discovery was made. In 1958, Vernon Ingram and J.A. Hunt sequenced the *HBB* gene, discovering that a point mutation (Glu6Val) was the molecular cause behind HbS.[30] Research into the mechanism of sickling red blood cells continued throughout the mid-1900s, but it was not until the 1970s that SCD awareness became a public health issue.[3]

In 1970, Dr. Robert Scott published an editorial in the *Journal of the American Medical Association*, avowing that SCA should be a public health concern in the United States.[3] Dr. Scott argued that this priority should be based on SCA's prevalence and severity in the US population, and that it should receive funding and support similar to that of other chronic health conditions, such as cystic fibrosis or diabetes.[3] He also described the fragmented nature of the various SCA support facilities throughout the United States. This last concern was improved by the formation of the National Association for Sickle Cell Disease in 1971.[31] Fifteen community sickle cell organizations gathered together in Racine, Wisconsin to form this association, which was renamed the Sickle Cell Disease Association of America (SCDAA) in 1994.[31]

In 1971, President Nixon included SCD in his health address to Congress.[32,33] In this address, President Nixon proposed raising the funding of SCA to $15 million in the 1973 fiscal year, which was a 15 fold increase over the budgeted amount in the prior fiscal year 1971.[34] Shortly after this address, Congress passed the National Sickle Cell Anemia Control Act of 1972.[33] This legislation offered educational activities for health care providers and the public, counseling and screening programs for SCD, and funded grants for research regarding the diagnosis, treatment, and management of SCD.[34]

Between 1972-1973, the National Sickle Cell Disease Program was founded and the National Heart and Lung Institute (NHLI) started funding SCD centers.[33] The NHLI also established its own sickle cell center soon after and was renamed the National Heart, Lung, and Blood Institute (NHLBI) in 1976.[33] The funding provided by the National Sickle Cell Anemia Control Act of 1972 helped make significant improvements in the management of SCD, including improving both lifespan and quality of life in individuals with SCD.[9] Some of these advancements

include pneumococcal vaccinations, preventative penicillin therapy, newborn screening for SCD, the development of hydroxyurea, and bone marrow transplantation.[35]

In 2003, the Sickle Cell Treatment Act was passed by Congress.[32] Signed into law in 2004, this legislation provided $10 million a year in funding to expand SCD treatment centers in the US and to help develop best practices in sickle cell care.[32] This funding expired in 2009 and has not been renewed.[36] Despite the initial support for SCD funding, optimal funding is currently lacking.[37] Legislation has been proposed for more federal funding, such as S.2465, the Sickle Cell Disease Research, Surveillance, Prevention, and Treatment Act of 2018.[36] This legislation was received by the US Senate. The Senate read it twice and then referred it to the Committee on Health, Education, Labor, and Pensions, where it currently awaits further action.[36]

Strouse et al[38] explored the association between PubMed publications and clinical trials and the funding of sickle cell disease and cystic fibrosis. Disease-specific funding was estimated using NIH RePORT, a tool that shows the annual support for various conditions and research topics.[38] Strouse et al[38] also examined the financial reports for the Sickle Cell Disease Association of America (SCDAA) and the Cystic Fibrosis (CF) Foundation and Cystic Fibrosis Foundation Therapeutics, Inc. Per person expenditures for individuals with either SCD or CF were calculated by using the estimated prevalence rates of each condition in the US.[38] Publications in PubMed, new clinical trials, and FDA approvals from 2009 to July 2013 for either condition were examined as well. Funding per individual with CF was 7.6 (2010) to 11.4 (2011) times higher than for SCD.[38] This funding included 3.5-fold higher funding from the National Institute of Health (NIH) and up to 440-fold higher national foundation funding.[38] Between 2010 and July 2013, five drugs were approved by the FDA for the treatment of CF in comparison to zero for SCD.[38] This study helps

quantify the disparity in funding for SCD in comparison to other genetic conditions of lower prevalence.

Hemophilia, a hereditary clotting disorder, offers another comparison to illustrate the disparity in funding for SCD. Hemophilia is estimated to affect 20,000 people in the United States,[39] compared to SCD which affects approximately 72,000 – 98,000 individuals in the United States.[11] Despite this difference, hemophilia currently receives more funding than SCD. For example, the World Federation of Hemophilia (WFH) receives financial support from several drug companies, including Pfizer, Bayer, Novo Nordisk, and Biogen.[40] Between May 2014 and May 2018, seven new drugs to treat hemophilia were approved by the FDA, while only one was approved for SCD.[41]

A lack of funding also affects the availability of transition and adult care for AYA and adults with SCD. The Cystic Fibrosis Foundation funds and accredits over 100 adult care centers in the United States, while the CDC's National Resource Directory lists only 44 adult care centers for SCD, and 14 centers who treat both children and adults.[42,43] The access to care for SCD varies greatly based on one's geographic location. For instance, Pennsylvania funds 9 total care facilities: 6 pediatric, 2 adult, and 1 pediatric and adult. There are seven states who fund neither a pediatric nor an organized adult care facility for SCD.[43] Fifteen states have a pediatric SCD center, but no adult care facility.[43] This likely means that individuals with SCD in these states are relying on their primary care practitioners to provide them with care for both general health and their SCD. It is also important to note that an individual could have access to a good site for SCD care, but if it is not a formalized program it will not be listed on the CDC's National Resource Directory. This demonstrates the limited access to specialized care for SCD in the US.

While newborn screening (NBS) helps identify newborns with SCD, which can be used to estimate the prevalence rate in the United States, there is little information known regarding specific details of prevalence numbers and locations for adults with SCD. Currently, no patient registry or centralized database exists for SCD. The aforementioned legislation, S.2465, includes a section on funding surveillance of SCD by distributing grants to SCD centers throughout the US to help them gather information about the prevalence and the distribution of SCD throughout the country.[36] These registries would also allow sites to assess outcomes and evaluate the success of certain interventions.[44]

The question of an implicit bias against individuals with SCD in the United States is raised after reading such evidence. Although it affects multiple ethnicities, a stereotype about SCD being a "black disease" has emerged in the United States.[45] Telefair et al[45] surveyed 227 multidisciplinary health care providers about the impact that a patient's race has on their medical care. Of the providers surveyed, 138 (61%) were female and 89 (39%) were male. 62% (141) were Caucasian, 29% (66) were African American, and 9% (20) identified as a race other than Caucasian or African American.

African American and Caucasian health care providers were found to have conflicting views regarding the influence of race on the delivery and quality of health care for individuals with SCD. A majority of African American health care providers (76%) agreed that race influenced the quality of care received, while only 35% of Caucasian health care providers thought that race influenced care. Providers were also asked if they thought patient race influenced decisions regarding pain medications. 42% of African American health care providers agreed, while only 16% of Caucasian health care providers agreed. When asked if the quality of relationships with patients was influenced by race, 71% of African American providers thought it was, while only

37% of Caucasian providers did. Overall, Telefair et al[45] found that both female health care providers, regardless of race, and African American health care providers were more likely to believe that race influences patient-provider relationships, decisions regarding pain medication, and the overall quality of care the patient receives. This can be contrasted with Telefair et al's[45] finding that Caucasian health care providers and male health care providers of all races were less likely to think race factored into these interactions and relationships.

These findings show that the race of individuals with SCD has an impact on the level of care they receive. Telefair et al[45] suggested implementation of continuing education for health care providers. This could help providers identify their own prejudices and how their own background influences their own medical practice. Creating a more culturally diverse staff and having staff members that are more culturally sensitive were also suggested as solutions to mitigate this problem.[45]

Smith et al[37] also addressed the disparity in health care for individuals with SCD. They suggested implementing a systematic approach to care for individuals with SCD, as well as an assessment of the variation in care for these individuals. The hope is that these steps will help alleviate disparities in care within the SCD community by providing all individuals with SCD the same level of care. Health care disparities still remain for individuals with SCD, but hopefully as these disparities are increasing acknowledged within the medical and health care community, they can be gradually be alleviated.

2.1.3   Newborn Screening

Newborn screening (NBS) is a state-based public health initiative that began more than 50 years ago.[46] In 1961, Dr. Robert Guthrie developed the first screening test for newborns.[9,47] Using

blood obtained from a heel prick shortly after birth, he screened for PKU, a genetic disorder that can cause permanent intellectual disability if a strict diet is not followed beginning immediately after birth.[47] In 1968, the World Health Organization (WHO) appointed James M.G. Wilson and Gunner Jungner to write a report to help guide decisions regarding screening for certain health conditions.[48] Wilson and Jungner developed a set of 10 criteria to aid in decisions revolving around population-based screening.[48] As the newborn screen was beginning to be implemented throughout the United States, there was debate among policy makers regarding which disorders should be included in their jurisdiction's screening.[49] In general, policy makers used the Wilson and Jungner criteria to help guide their decisions and focused on adding treatable disorders that had a higher prevalence and would save the state money by their early detection and treatment.[49]

Today, all 50 states, as well as the District of Columbia, each have their own state newborn screening program. Each state's newborn screening program is run differently, and it is up to the state's public health department and/or state legislature to decide which conditions are included on the NBS. Until 2006, there was no uniformity in the conditions screened for by each state.[46] This discrepancy between states was due to several limiting factors, including access to new screening methods and availability of state resources to fund testing.[46] Over time, it became apparent that various policy issues at a state level were interfering with the NBS program.[49] In 1999, the Health Resources and Services Administration (HRSA) sponsored the American Academy of Pediatrics (AAP) to establish a NBS task force to help examine these challenges.[50] This task force outlined an agenda to help resolve some of these issues, one being the lack of standardization among states regarding which conditions were included on the NBS.[50]

As a response to the issue of uniformity, in 2006 the Maternal and Child Health Bureau (MCHB) commissioned the American College of Medical Genetics (ACMG) to help outline

national NBS standards and to compose a list of recommended conditions that should be on every state's testing panel.[46] The ACMG included conditions that met the following criteria: 1) the condition had an available screening test, 2) the condition had an effective treatment, and 3) the course of the disease was known.[46] The ACMG criteria were similar to the Wilson & Jungner criteria that were created 40 years prior to the development of the Recommended Uniform Screening Panel (RUSP). The RUSP is a list of genetic conditions that the Secretary of the Department of Health and Human Services recommends states include on their NBS.[51] These conditions are reviewed by the Advisory Committee on Heritable Disorders in Newborns and Children, with the goal being to provide states with a standardized list of conditions that meet the aforementioned ACMG criteria.[51] Ultimately, each state can decide whether or not to screen for a particular condition, and some states screen for additional conditions.[51] Currently, as of May 2018, thirty-four conditions are included on the RUSP.[51]

2.1.4   Newborn Screening and Hemoglobinopathies

Sickle cell anemia (HbSS), hemoglobin C disease (HbSC), and sickle cell-beta thalessemias (HbS/β-Thal) are included on the RUSP in the United States.[51] Additionally, various other hemoglobinopathies are included on the RUSP for Secondary Conditions.[51] New York was the first state to screen for hemoglobinopathies starting in April 1975.[9] Gradually, over the next 30 years, the remaining 49 states and the District of Columbia added this category of screening tests to their list of mandatory conditions.[9]

In 1986, a study by Gaston et al[52] elucidated the benefits of administering penicillin to children with SCD shortly after birth. This study showed that penicillin helped reduce mortality in infants and children with SCD under three years of age by helping to prevent invasive

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pneumococcal disease and death.[52] When newborns are born their hemoglobin consists primarily of HbF, which provides a protective effect against the sickling hemoglobin until 4-5 months of age.[53] Because of the presence of HbF during these first months of life, routine CBCs or clinical exams cannot make an accurate diagnosis of SCD, since presumably both would appear to be normal.[53] Additionally, the risk of death from sepsis begins at four months of age, which was also well before a diagnosis of SCD would be made clinically in the mid to late 1980s.[35] Because of this risk, the impetus to diagnosis SCD shortly after birth in order to implement prophylactic penicillin and provide education on fevers in order to prevent death from pneumococcal sepsis was not realized before Gaston et al's 1986 study.

In response to these research results, the National Institute of Health (NIH) hosted the "NIH Consensus Development Conference on Newborn Screening for Sickle Cell Disease and Other Hemoglobinopathies" in April of 1987.[54] This conference included a variety of stakeholders, including professionals in the fields of genetics, hematology, public health, pediatrics, law, and epidemiology.[54] Health professionals, as well as individuals with SCD, parents of children with SCD, and other interested parties participated in conference discussions. The main goal of this conference was to answer several questions regarding NBS, follow-up, and research directions in the field of SCD. Universal screening for hemoglobinopathies in all newborns was one of the main recommendations generated by the conference, which was in response to the demonstrated benefit of early intervention shown by Gaston et al's study.[54]

Many states added SCD to their list of required conditions after this conference consensus statement was published.[55] While the NIH Consensus panel recommended universal NBS for hemoglobinopathies instead of the previously adopted high-risk screening that some states followed, the panel recommended that only some states adopt universal NBS.[54] When making this

recommendation, the panel did not clarify which specific states should adopt universal NBS for hemoglobinopathies, or define what would be considered a "high risk" population. Targeted screening was suggested as a possible alternative to universal screening in states where there were few "at risk" members.[54] Over the years, states gradually added SCD to their universal NBS. New Hampshire was the last state to add hemoglobinopathies to their NBS in May 2006, in response to the implementation of the RUSP that year.[9]

The early detection of SCD is essential for decreasing morbidity and mortality within the SCD population.[56] The administration of prophylactic penicillin as well as timely management of splenic sequestration and/or fever are all reasons in favor of screening newborns for SCD and other hemoglobinopathies.[56] Because of these early interventions and improved management and care of individuals with SCD, survival into adulthood has increased considerably over the past 40 years.[5] The median survival for HbSS disease was around 20 years in the 1970s[3] and is currently around 42-48 years.[4] Because the lifespan of individuals with SCD has increased, there is a need for transition care for this population.

2.1.5   Newborn Screening for SCD in Pennsylvania

Universal NBS for SCD became available in Pennsylvania in September 1992.[9] This test consists of a heel-stick, ideally around 48 hours of age, with an acceptable range of 24-72 hours.[57] The blood from the heel-stick is transferred to a filter paper, which is sent to the proper laboratory for analysis.[57] For SCD, the state is divided into six different geographic regions and six sickle cell centers are contracted with the Pennsylvania Department of Health to provide follow up for abnormal or inconclusive newborn screening results.[58] In Pennsylvania, there is a recommended course of action that should be followed when there is a positive newborn screen for a

hemoglobinopathy.[57] This order of actions is determined by the Division of Newborn Screening and Genetics Bureau of Family Health within the Pennsylvania Department of Health.[57]

First, the primary care provider (PCP) listed on the blood spot filter paper is contacted with the abnormal test results, as is the sickle cell referral center in the area. All abnormal hemoglobin results are sent to a sickle cell referral center in Pennsylvania.[59] All counties in Pennsylvania are covered by the six sickle cell centers in the state.[59] If the PCP has not contacted the referral center within two weeks of the results, it is the referral center's responsibility to contact the PCP to help schedule any necessary confirmatory testing and discuss the best manner in which to schedule an appointment with the patient. The referral center is also responsible for informing the family and PCP that the center can provide medical and psychosocial management for the infant. This support could include direct aid to the PCP in the form of conference calls or in-person meetings. If the referral center is unable to schedule an appointment with the family within two weeks of the initial referral, then they must notify the Newborn Screen Follow-up Program (NSFP) Community Health Nurse. They must also notify the NSFP Community Health Nurse when a patient misses his/her appointment during the diagnostic period. There are six centers for newborns with SCD in Pennsylvania and one of the centers is located in Pittsburgh.[60] In Pittsburgh, the Pediatric Sickle Cell Clinic at the Children's Hospital of Pittsburgh is responsible for 20 counties within the Western Pennsylvania region.[60]

When a newborn has a type of sickle cell trait that is identified on the newborn screen, a different process is followed. A family letter is sent by the sickle cell center that relays information about the specific trait that has been identified, such as Hemoglobin S trait or Hemoglobin C trait. This letter also includes an educational brochure with more information about the trait that was identified and also includes information about reproductive risks involved with sickle cell trait.

For babies born in Western PA, the letter includes the telephone number for the Sickle Cell Clinic at the Children's Hospital of Pittsburgh of UPMC (CHP) and encourages parents to call with questions or to schedule a clinic appointment as follow up. The PCP is notified in the same process as noted above.

2.2   MANAGEMENT OF SICKLE CELL DISEASE

2.2.1   Management of SCD from Infancy through Childhood

The complications of SCD may first appear within the first year of life, occasionally as early as 4 months of age when the risk of death from pneumococcal sepsis can occur in an otherwise healthy appearing infant.[61] The symptoms and clinical manifestations can vary between individuals with SCD; some individuals exhibit milder features while others are more severely affected.[61] Newborns are born with fetal hemoglobin (HbF), which is formed from alpha and gamma chains, rather than the beta chains that are the chains affected in SCD. While fetal hemoglobin may provide a temporary protective effect against the signs and symptoms of SCD during the newborn period, the amount of HbF typically starts to wane around 4 to 5 months of age, making early detection and intervention important.[53] The first symptoms that infants may display include pneumococcal sepsis, dactylitis, anemia, and splenomegaly.[57] The goal of newborn screening is to diagnose infants with SCD as early as possible to help prevent early complications of the disease before any symptoms are present. For this reason, timely NBS follow-up from the PCP and the local sickle cell clinic is critical. Early preventative measures for SCD in the infancy period include the administration of several vaccines, including an annual flu vaccine beginning

at sixth months of age, as well as a series of pneumococcal and meningococcal vaccines.[1] Until two years old, infants with SCD follow the same immunization schedule as other infants without a diagnosis of SCD.[1] Prophylactic penicillin, starting by 2 months of age, is recommended for infants with SCD, as well as the education of parents and caregivers regarding the danger of sepsis when a fever occurs in the infant.[1]

Splenic sequestration crises and infection are the leading causes of death in children with SCD.[62] Splenic sequestration occurs when RBCs become trapped in the spleen, causing the spleen to enlarge.[63] During severe episodes of splenic sequestration, an individual's hemoglobin level may drop greatly and quickly, which can cause hypovolemic shock (a decrease in the volume of blood plasma) and death.[63] Children with SCD are at 300-500 times higher risk than the general population to develop pneumococcal disease; this risk is highest between ages 1-4.[64] This increased risk is a result of the loss of splenic function, which may be caused by tissue death from sickling, vaso-occlusion, and sequestration events within the spleen. This causes the spleen to be poorly functional, which lowers its ability to kill encapsulated organisms and promotes acute sequestration of blood.[64] Education of parents and health care providers to help recognize the signs of splenic sequestration (including splenomegaly and acute severe anemia) can help prevent death.[64]

In 1983, the NHLBI established the Prophylactic Penicillin Study (PROPS) to help assess the efficacy of penicillin in preventing pneumococcal infections in children with SCA.[52] The PROPS clinical trial was a randomized, double-blind study that took place at 23 clinical sites throughout the US. Participants included children, ages 3 months – 3 years-old, who had been diagnosed with SS disease and were 1) not exhibiting signs or symptoms of infection 2) not receiving long-term transfusions or antibiotics and 3) had no known allergies to penicillin.

Participants were randomly assigned to the experimental (penicillin) or control group. Children in the experimental group received 125 mg of penicillin V potassium twice a day. Children in the placebo group were administered 50 mg of vitamin C, which was administered at the same frequency. The vitamin C and penicillin tablets were similar in appearance to help maintain the double-blinding of the study. A physical examination and a complete blood count were done every three months. Urine samples and pill counting were completed to help determine participant compliance in taking the medications. The study was ended eight months early after an 84% reduction in pneumococcal infection was seen in children who were taking the penicillin. No deaths were caused by by pneumococcal sepsis in the penicillin group, while three deaths were observed in the control group.[52] The results of this study lead to the NHLBI's recommendation that all newborns with HbSS disease should be administered prophylactic penicillin by four months of age.[54] After this recommendation in 1986, mortality caused by infections in children with SCD markedly decreased.[62] A study by Manci et al[62] that examined cause of death in SCD showed that in autopsies performed before 1978, infections accounted for 46.6% of deaths, which occurred primarily in children under 3 years of age (57%). After 1985, there was a dramatic decrease in infectious deaths in those under age 3, which helps demonstrate the measurable impact that early diagnosis, prophylactic penicillin, and the management of fevers had on the death rate in SCD.[62]

Another common cause of mortality or morbidity in children with SCD are cerebrovascular accidents (CVAs) or large vessel stroke.[65,66] By age 20, approximately 11% of children with HbSS disease experience a stroke.[67] Part of this risk can be reduced by the use of Transcranial Doppler (TCD), which can help identify children at risk for stroke.[67] TCD is a type of ultrasound that measures the speed of blood flow through the blood vessels of the brain by measuring the echoes of the ultrasound waves that are moving through the brain. Annual TCD is recommended for

children with HbSS disease and HbS/β^0-Thal disease starting at age two.[1] Children who have abnormal activity on their TCD, meaning an elevated velocity of 200 cm/sec or more, compared to the reference range of 170 cm/sec, are shown to be at higher risk for stroke.[68] If abnormal TCD activity is identified in a child, chronic transfusions effectively reduce the risk of primary stroke.[67] Chronic transfusions have been shown to reduce the risk of an initial stroke in children with SS disease with abnormal TCD results by more than 70%.[67] TCDs are an important preventative measure for monitoring and preventing strokes in individuals with SCD.[67,68] While this literature review focuses on interventions that have reduced mortality in infants and children with SCD, there are many other recommendations for the care of individuals with SCD. The NHLBI's Report on the Evidence-Based Management of Sickle Cell Disease serves as a reliable resource for physicians and other health care professionals regarding the management and care of individuals with SCD.

2.2.2   Adolescents and Young Adults with SCD

The AYA period for individuals with SCD is one marked by an increase in both morbidity and mortality. Hamideh and Alvarez[69] used data from death certificates available from the CDC to compare mortality rates in children with SCD from 1979-1998 to 1999-2009. Mortality rates decreased by 61% in infants, by 67% in children ages 1-4 years old, and by 22-35% in children ages 5-19 years old.[69] In addition to comparing overall mortality rates during these two periods of time, Hamideh and Alvarez also looked at the mortality rates in specific age groups within each set of data. In the data from 1999-2009, the mortality rate in the 15-19 year old age group was 0.6 per 100,000 individuals, compared to 1.4 per 100,000 individuals in the 20-24 year old age group.[69]

This period of increased mortality (15-24) corresponds with the ages individuals with SCD typically transition from pediatric to adult care.

Quinn et al[5] conducted a cohort study that evaluated the changes in causes and timing of death in individuals with SCD and found that the burden of mortality had shifted to AYA. The Dallas Newborn Cohort (DNC) that was studied was comprised of children followed for their SCD since birth, starting in 1983. At the time of the study, in 2010, the DNC included 940 subjects, with a mean follow-up time of 9.4 years for each subject. Patients in the DNC range from newborns to age 18, at which age the patient is transferred to the adult sickle cell center. The cohort was 51.8% male and 49.2% female and included HbSS (61.2%), HbSC (30.2%), HbS/β^+-Thal (6.7%), and HbS/β^0-Thal (2.2%). The highest incidence of death in the DNC was in patients who were 15 years or older. Since their last analysis of the cohort in 2002, seven individuals had died. Six of the seven deaths in the cohort occurred in individuals who had transitioned to adult care within the past two years. In deaths that occurred in the cohort from 1983-1990 and from 1991-2000, the median ages of death were 3.0 years and 3.1 years, respectively. In the deaths that occurred in the DNC from 2001-2007, the median age of death increased to 17.1 years. This increase is likely due to the implementation of newborn screening, which would have shifted the burden of mortality to AYA. AYA who had recently transitioned their care from the pediatric to adult care facility were at the highest risk for death.[5,70] Possible explanations for the increase in mortality during the AYA period include an unsuccessful transition from pediatric to adult care, as well as the possibility that the buildup of organ damage that has occurred since birth is beginning to manifest itself during this AYA period.[64] Because SCD is a chronic disease, it may be more likely that inconsistent care is contributing to poor outcomes in AYA with SCD.[71]

Blinder et al[71] conducted a retrospective longitudinal cohort study that evaluated health care resource utilization as well as costs to pediatric and adult patients with SCD, focusing especially on the transition period. Medicaid data from health care administrative claims from five states was obtained for analysis. Using this data, outpatient, inpatient, and ED visits, as well as their associated costs, were estimated for each of the 3,208 patients in the study.[71] Patients were observed for an average of 6.5 years, and 20.4% of patients were observed through their transition to adult care at age 18.[71] Among patients eligible for iron chelation therapy (ICT) (greater that 10 transfusions), this study assessed health care costs for individuals who were chronically transfused and appropriately received iron chelation therapy (ICT) and health care costs for individuals who did not receive ICT, even though it was indicated, suggesting noncompliance or inadequate access to care. In both groups, total quarterly health care costs were higher post-transition than pre-transition. The ICT group's cost averaged $11,050 pre-transition compared to $12,966 post-transition, and the non-ICT group's cost averaged $6,762 compared to $14,511, post-transition (P<0.001).[71] The frequency of emergency department (ED) visits was also found to increase in both groups post-transition, which could explain the increase in quarterly health care expenditures. In the ICT group, ED visits were 0.87 per quarter pre-transition vs. 3.37 post-transition and in the non-ICT group, ED visits average 1.18 per quarter pre-transition and increased to an average of 6.13 post-transition.[71] Blinder et al[71] suggested that these increases could be caused by decreased follow-up and preventative care in AYA. This study's findings help to demonstrate the shift from preventative to symptomatic care that an AYA with SCD may experience after transitioning to adult care and the accompanying burden on the health care system.

Brousseau et al[72] conducted a retrospective cohort study on emergency department (ED) visits and hospitalizations for SCD using state inpatient and ED databases in eight geographically

diverse states, together totaling 33% of the US population with SCD. This study looked at ED and hospital stays that were specifically categorized as sickle cell-related using ICD-9 and Clinical Classification Software codes.[72] Hospital stays and ED visits that were not related to SCD were removed from the analysis.

This study included 21,112 patients, who had a total of 109,334 encounters, averaging 2.59 (95% CI, 1.48-1.55) encounters for hospital stays and 1.08 for ED visits.[72] Of these patients, 7,250 were between the ages of 18 to 30 years old. Among all of the age groups, 18 to 30 year olds were found to have the highest utilization rates and averaged 3.61 visits per year.[72] 22% (1594) of the individuals who were 18-30 years old has 3-10 acute care encounters a year, in comparison to 12.6% of 10 to 17 year olds.[72] 7.4% (530) individuals in the 18 to 30 year old age group had 10 or more acute encounters, in comparison to only 1.1% of the 10-17 year old age group. This helps demonstrate the increase in morbidity during the AYA age period.

The 18-30 year old age group also had the highest rehospitalization rate, with 41.1% being rehospitalized within 30 days and 28.4% within 14 days, compared to the group average of 33.4% and 22.1%, respectively.[72] Proposed solutions to the higher rates in this AYA group include increased access to care and more comprehensive transition programs to help reduce morbidity during this period of time.[72]

These studies help explain some of the issues facing AYA with SCD. Adolescence and young adulthood remain a high-risk period for individuals with SCD. In response to this need, transition programs are being developed to ensure that AYA are ready for this transition of care.[73]

2.2.3 Summary of General Management for SCD

Management of SCD is both preventative and symptomatic. SCD affects many of the body's organ systems and can result in multiple health concerns. The NHLBI created an expert-panel report that delineates specific management guidelines to help health care providers care for individuals with SCD. The most recent version of this report was published in 2014. The goal of this report is to provide recommendations for care based on scientific evidence.[1] These guidelines specify many preventative measures that help prevent progression of the disease and provide suggestions for preventing the complications of SCD, including renal disease, stroke, pulmonary hypertension, strokes and pneumococcal infection.

Typically, individuals with SCD see a hematologist regularly who can help manage prevention and treatment of the disease. As individuals with SCD require close follow up with a variety of other health professionals, the hematologist often makes referral to other specialties, which commonly include dentists, ophthalmologists, pulmonologists, and behavioral health specialists.[1] In addition to following with a hematologist, individuals with SCD also follow with their primary care provider (PCP) for regular checkups. This helps ensure that individuals with SCD are receiving specialized treatment/management related to their SCD, as well as routine screenings provided by their PCP.

2.2.4 Available Treatments for SCD

In 1998, Hydroxyurea (HU) became the first FDA-approved drug for SCD.[74] HU is recommended for individuals with HbSS disease and HbS/β^0-Thal.[1] There have been no phase III clinical trials for HU in the management of other types of SCD.[1] The clinical trial that proved its

efficacy was a double-blind, randomized study that included 299 participants (49.5% male, 51.5% female) at 21 clinical sites throughout the United States.[74] Of the participants, 295 had a diagnosis of HbSS disease and 4 had HbS/β^0-Thal.[75] Eligibility criteria included men and women ages 18-50, who had been hospitalized or gone to the emergency room at least three times in the year prior to time of recruitment for pain crises related to SCD.[75] The study was stopped early after only 24 months, due to the proven efficacy of the medication.[74]

Folic acid was given to all participants for the first four weeks of the study.[74] At this point participants were randomly assigned to 1) a control group or 2) the treatment group. The control group was given a placebo (a starch pill) and the treatment group was given hydroxyurea, initially at 15 mg/kg/day.[74] The dose was increased 5 mg/kg/day every 12 weeks, unless signs of bone marrow suppression were shown. The dose of placebo was increased in a similar manner, in order to maintain the double-blind nature of the study. In addition, all participants received 1 mg of folic acid per day. Participants were seen every two weeks, and blood samples were obtained and analyzed to assess the amount of fetal hemoglobin in the blood.[74]

In this clinical trial, Charache et al[74] found that the average time until a vaso-occlusive event was longer (3.0 months) in patients with SCD who were treated with HU, compared to the untreated group (1.5 months), with all values being statistically significant. The trial participants who received HU developed acute chest syndrome less regularly, needed less frequent transfusions, and fewer units of blood when a transfusion was warranted.[74]

Hydroxyurea increases the amount of fetal hemoglobin in the red blood cells, which makes the RBCs less likely to sickle due the increased amount of oxygen in the RBCs.[76] It was originally developed as a chemotherapy drug, and has been used to treat leukemia, melanoma, and ovarian cancer.[77] Hydroxyurea was initially only approved for adults with SCD and moderate to severe

pain crises. Nearly 10 years went by before hydroxyurea was officially approved for use in children, though its efficacy in treating children had been demonstrated since 1996.[78,79]

It was not until December 21, 2017, that the FDA approved hydroxyurea for use in pediatric patients with SCD.[78] A major influence behind its approval was the BABY HUG clinical trial.[80] This was a multi-center, randomized, double-blind phase III clinical trial of HU in infants who were initially between 9-18 months old. All participants had a diagnosis of either HbSS disease or HbS/β^0-Thal. The study began in October 2003 and concluded in September 2009. A total of 193 subjects were randomized to either HU (20 mg/kg/day) or the placebo. The study found that HU was associated with significantly lower rates of dactylitis, acute chest syndrome, hospitalization, and initial and repeated episodes of pain.

Another clinical trial that helped drive HU's approval for use in children was called the European Sickle Cell Disease Cohort study.[81] A total of 432 pediatric patients participated in the study, ages 2-18. 141 (32.6%) of children in the study had not been treated with HU prior to the study.[78] HU was found to increase HbF in the blood and to decrease the frequency of complications related to SCD, including acute chest syndrome, vaso-occlusive episodes, and hospitalizations, after it had been taken for 12 months.[78] Side effects of hydroxyurea in children can include bone marrow suppression including neutropenia, headache, gastrointestinal distress, and dermatologic changes such as hyperpigmentation.[79] There have been no reports of long-term toxicity, but maintaining the proper dose is important to prevent any severe side effects.[81–83]

While the NHLBI guidelines recommend that individuals with HbSS disease and 3 or more moderate to severe pain crises take hydroxyurea, it is thought that hydroxyurea is underutilized by this population.[84] Stettler et al[84] analyzed de-identified commercial health and pharmacy claims from the Optum Normative Health Informatics database to identify individuals over 18 years of

age who had one or more outpatient or inpatient claims and probable HbSS based on the ICD codes that identified the encounter. More specifically, patients were selected for inclusion if they had three or more emergency department visits, hospitalizations, or both over the past year that included one of the five most common ICD codes for patients with HbSS disease who were experiencing a pain crisis, such as ICD code 517.3, which indicates HbSS disease with acute chest syndrome.[84] Hydroxyurea use was defined as the filling of one or more prescriptions for hydroxyurea after the third encounter in the ED or hospital.[84] 2,086 individuals (18 years or older) were identified with probable HbSS disease.[84] 32.5% of this identified patient population had at least three hospitalizations or ED visits in the past year, and within this population, only 15.1% had been treated with HU within three months of their third encounter.[84] At 12 months, this coverage increased to 22.9% (p=.002).[84] These results suggest that HU is underutilized by a patient population that could benefit from its use, and that only one quarter of patients who could benefit are taking it. This study did not include all patients who could benefit from HU therapy, only those with HbSS disease, and did not include uninsured or publicly insured individuals.[84] Individuals who resolved their pain crises without admission to the hospital or presentation to the ED were not included either. [84]   All of these factors could affect the generalizability of the data. Factors that have been thought to impact this underutilization include lack of shared decision making with the patient, lack of physician training, and a fear of adverse events from the patient.[1]

Endari (L-glutamine oral powder) is the second drug therapy approved for the treatment of SCD. It was approved by the FDA on July 7, 2017 and will soon be available in the US.[85] Endari is approved for individuals over five years old and can also be used in conjunction with hydroxyurea.[85] Endari works by increasing the amount of free glutamine that moves around in the blood stream. This circulating glutamine can be captured by sickled red blood cells, which

normally have a deficiency of glutamine. When the glutamine is broken down by these cells, antioxidants are released, which help lower oxidative stress in the sickled cells. This reduction of oxidative stress within the cells allows more oxygen to be delivered throughout the body and in effect, can help lessen pain and make the RBCs less likely to become lodged within blood vessels.[86]

Glutamine has been considered a potential treatment for SCD since the mid-1990s. The first study related to glutamine and SCD was in 1998, which showed that glutamine reduced the red cell adhesion rate.[87] Seven participants with SCD (ages 19-60 years old) with a diagnosis of HbSS disease participated in this study.[87] Exclusion criteria included current or previous treatment with hydroxyurea, having undergone a blood transfusion in the past 3 months, and pregnancy.[87] Baseline blood samples were obtained, as well as samples at the conclusion of the study. 10 g of L-glutamine were administered three times a day to participants for four weeks.[87] The results showed an increase in NAD redox potential, which was thought to reduce the oxidative damage that occurs in sickled RBC.[87] All of the participants reported decreased levels of chronic pain and 6 of the 7 reported decreased drug-use to control their chronic pain, though this was not a controlled clinical trial so all participants knew they were being administered a drug that was supposed to treat SCD.[87] Glutamine may also reduce the number of pain crises and the frequency of acute chest syndrome.[85] Patients also had fewer hospitalizations and shorter hospitalizations overall when administered glutamine as treatment.[85]

The clinical trial for Endari was a randomized, double-blind, multicenter study that included 230 participants. Inclusion criteria included participants who were at least 5 years old, had a diagnosis of SCD or HbS/β^0-Thal, and had at least two documented episodes of sickle cell crises within 12 months of recruitment. In addition, if an eligible participant was receiving stable hydroxyurea treatment, he/she remained on that course of treatment throughout the clinical trial.

Participants were randomly assigned to the experimental or placebo group. Individuals in the experimental group received 0.3g/kg of L-glutamine, administered orally twice a day for a total of 48 weeks, with an upper limit for a daily dose set at 30 grams. The drug was in powder form and could be mixed with water or other cold beverages (excluding alcohol, carbonated, and acidic beverages), as well as certain foods, such as applesauce or yogurt. The control group received 0.3g/kg of the placebo (100% maltodextrin), which was also administered twice a day orally for 48 weeks, with the same limitations, dosage increases, and mixing instructions as the experimental group. At the end of the 48-week period, the drug and placebo were tapered off to zero over the course of three weeks.[88] Over the 48-week clinical trial period, those in the experimental group experienced fewer sickle cell crises (3) compared to those in the control group (4), as well as fewer and shorter hospitalizations, and a lower incidence of acute chest syndrome. Side effects from L-glutamine therapy included headache, abdominal pain, cough, back and chest pain, nausea, and constipation.[85] Of note, results from the randomized controlled trial have not yet been published and the preliminary data suggest only a modest benefit. Thus, while Endari is clinically indicated to help reduce acute complications of SCD in individuals who are 5 years or older, its role in general SCD management is yet to be determined.[89]

The only current cure for SCD is a hematopoietic stem cell (bone marrow) transplant (HSCT). The limiting factors to HSCT include the need for a suitable bone marrow donor and an unclear risk-to-benefit ratio.[90] A suitable donor must have the same human leukocyte antigen (HLA) type as the receiver of the transplant.[91] HLA types are inherited, so siblings are often a common source of complete matches.[91] Less than 20% of individuals with SCD have a sibling who is a HLA match.[92] Overall, the disease-free survival rate with an HLA-identical sibling donor is 85%, as complications such as transplant-related mortality (7%) and graft failure (9%) can

occur.[90] There are now increasing numbers of clinical trials looking at alternative donors outside of a perfect match sibling.[93] This includes umbilical cord hematopoietic stem cells, unrelated donors such as from the international bone marrow transplant registry, and partial match donors, including half match such that a parent and more sibling options would be potential sources for cure by transplant.[93]

Because of SCD's prevalence and its monogenic origin, gene therapy has long been proposed as a potential cure for SCD.[94] In 2001, gene therapy for SCD was performed and sustained in mice models.[95] This was achieved by the transfer of a modified *HBB* anti-sickling variant.[95] More recently, from 2015-2017, a team of medical professionals in France performed the first successful course of gene therapy in a human that cured SCD.[96] This case was a 13-year-old boy with HbSS disease whose red blood cells show no signs of disease, and who no longer requires transfusions or medicine to manage his SCD following gene therapy.[96] This case report has been cited as a proof-of-concept for larger clinical trials for SCD gene therapy. There are several other clinical trials currently recruiting or actively running for gene therapy and SCD or beta thalassemia.[97,98] The prohibitive cost of the course of gene therapy treatment is a concern, as this could limit access to those in developed nations and with the means to pay for it.[99] Because HSCT is currently the only proven cure for SCD and is not widely available or elected based on the aforementioned limiting factors, prevention and management of the complications of SCD is critical.

2.3 TRANSITION OF CARE

2.3.1 Transition

Transition can be defined as "the purposeful, planned movement of adolescents and young adults with chronic physical and medical conditions from child-centered to adult-oriented health-care systems."[100] Transition has become an increasingly relevant topic. Due to improved outcomes and prolonged lifespans for individuals with chronic diseases, there is a great need for adult care providers available to treat these individuals as they mature. Greater than 90% of children with chronic health conditions will live into adulthood.[101] A few examples of chronic health conditions that require life-long care include SCD, diabetes, asthma, congenital heart disease, and cystic fibrosis.

Adolescence is normally a time of transition for all children, but children with chronic diseases face additional challenges. Not only must children with chronic health conditions eventually take over responsibility for their health from their parent/caregivers, but they also typically transfer their care to an entirely new facility.[102] It is important to distinguish "transition" from "transfer." While transition refers to the active process of AYA moving from their former pediatric care facility to an adult care provider, transfer refers to the formal transfer of care between any two providers.[101] One can be transferred without first undergoing a coordinated transition process.

In 2002, a consensus statement published by the American Academy of Pediatrics (AAP), the American Academy of Family Physicians (AAFP), and the American College of Physicians (ACP) emphasized the importance of providing widespread, continuous care to AYA as they transitioned between pediatric and adult focused care providers and medical programs.[103] Together

these professional societies published a revised statement in 2011 that reiterated their original goals, as implementation of comprehensive transition care had not yet been achieved in the years that followed their original consensus statement.[104]

2.3.2   Barriers to Transition

Common challenges that AYA face when transitioning to adult focused health care providers include barriers related to beliefs and expectations about transitioning, relational challenges, barriers relating to knowledge regarding a health condition (AYA and/or provider), and issues of access to both health care and insurance.[105]

Rutishauser et al[106] evaluated the expectations of AYA and their parents regarding transition. This cross-sectional study included 318 parents of 283 AYA with chronic health conditions, ages 14-25, who had not yet transferred to their adult health care provider.[106] The greatest identified barriers to transition were: 1) their current comfort with their pediatric provider (37.5% of parents and 44.5% of AYA), 2) anxiety caused by their unfamiliarity with the adult provider (24% of parents and 20.1% of AYA), and 3) a lack of knowledge about the adult provider (26.5% of parents and 18.4% of AYA).[106] Their lack of knowledge regarding the adult provider and the idea that they would be leaving a comfortable environment for a foreign one, may have induced feelings of anxiety when thinking of their own or their child's transition of care.[106]

The end of a familiar, long-term relationship with one's pediatric provider has been commonly identified as a barrier to transition. Agarwal et al[107] surveyed pediatric endocrinologists regarding barriers faced during transition for AYA with type 1 diabetes. A total of 164 pediatric endocrinologists were surveyed, representing 32 US states.[107] 73.7% of respondents cited the termination of a long-held therapeutic relationship as a barrier to transition and 31% identified this

as a main barrier to transition.[107] Proposed solutions to help ease this transition to a new provider have included frequent communication between the pediatric and adult care facility, a documented transition plan, and early transition planning, including a meeting between the patient/family and the adult provider prior to transfer.[104,107,108]

In the survey by Rutishauser et al[106], when asked if their pediatric care providers had mentioned transferring to an adult health care facility, only 51% of youth ages 14-25 reported discussing this topic with their provider. In the 2005-2006 National Survey of Children with Special Health Care Needs, parents/guardians of 18,198 AYA (ages 12-17) were asked if they discussed the following with their child's care provider: 1) their child's anticipated need for an adult care provider, 2) their child's future health care needs as an adult, 3) changes in health insurance that may occur when transferring to adult health care and 4) encouraging autonomy in their child.[108] Discussing all four of these topics with the child's parent meant that the provider met the transition "core outcome" of the study. Per parent/guardian report, 42% of pediatric providers had discussed transferring to an adult care provider, 62% had discussed the child's health care needs as he/she becomes an adult, 34% had discussed changes in health insurance, and 78% had encouraged autonomy in the child.[108] Overall, 41% of youth ages 12-17 with special health care needs were found to meet the core transition outcome of the study.[108] This number helps indicate that while some youth with special health care needs are meeting this core outcome, the majority of the youth did not meet this goal, and a continued focus on transition care may still be needed to optimize the transition process.

While there are barriers that span the broad spectrum of chronic diseases, each chronic disease has its own unique set of barriers. Vijayan et al[109] interviewed AYA who had been infected with HIV perinatally, along with their parents/guardians and pediatric providers regarding their

thoughts on transition. The study included 18 AYA (ages 12-24), 15 parents/guardians, and nine pediatric care providers.[109] The data was collected through open-ended interviews with participants in the study. Identified barriers to transition included stigma associated with HIV, as well as a perceived or actual lack of autonomy.[109] The stigma associated with the disease was shown to be related to whether an AYA took his/her medications, and also negatively affected his/her sexuality, if/how he/she disclosed his/her HIV status, and the level of trust with their adult care provider.[109]

Overall, while an important issue, transition to adult care still faces many challenges in its successful implementation. Engaging all parties, including patients, parents/guardians, as well as pediatric and adult care providers has often been mentioned as a solution to help alleviate any miscommunications or misbeliefs that are encountered before or during the transition process.[110] In addition, the importance of the development of disease-specific transition programs and of assessing patient transition readiness earlier, have been cited.[110] While the transition process of patients with chronic diseases has made significant progress in recent years, there is still much improvement to be made.

2.3.3   Transition for AYA with SCD

While many AYA with chronic health conditions face similar barriers to transition[105], AYA with SCD face a few unique barriers when transitioning from pediatric to adult care. Andemariam et al[2] conducted a retrospective study of their transition program, a partnership between the pediatric sickle cell center at Connecticut Children's Medical Center and the adult care facility at the University of Connecticut Health Center to assess clinical and non-clinical risk-factors that were related to an unsuccessful transition. The study included 47 AYA, ages 16 and older who had

participated in the facility's transition program over the past five years. Older age at the time of transition was associated with poorer transition outcomes, which was identified as a novel risk factor. 77% of AYA who transitioned before age 21 successfully transitioned, compared to 21% of patients who completed a successful transition after the age of 21 (P=0.008).[2] Andemariam et al[2] mentioned that because the implementation of their program had occurred in the past five years, transition of patients over the age of 21 was unavoidable, but could be prevented in the future since the program had already transitioned all older AYA who were present at the start of the program. Interestingly, the researchers also found that AYA with a milder SCD phenotype (e.g. HbSC or HbS/β^+-Thal) were less likely to have a successful transition than AYA with a more severe phenotype (e.g. HbSS or HbS/β^0-Thal).[2]

Stollon et al[111] conducted qualitative interviews with 13 pediatric and adult providers for individuals with SCD. From these interviews, the researchers identified health disparities that impacted AYA's ability to transition successfully, including poverty, education level, and access to health care.[111] Providers argued that these various sociodemographic factors were in competition with the transition process and often won out over transition. One provider said that "[AYA] are at risk … [their] coping skills are not good and the social supports are not in place."[111] AYA with SCD are a unique population, in that they are disproportionately affected by the aforementioned sociodemographic factors.[111] Other research regarding transition has identified similar discrepancies in transition support programs for African American and Hispanic AYA.[112,113]

Perceived readiness to transition is also an important factor in the transition process. Speller-Brown et al[8] assessed readiness in both transitioning AYA with SCD and their parents in a descriptive correlation study assessing the correlation between parent and AYA response. The sample included 60 AYA (14-21 years old) and their parents (N=60).[8] One parent per AYA was

interviewed. This parent was a guardian who had most often accompanied the AYA to the clinic or hospital. Surveys were administered during an outpatient clinic visit or during an inpatient admission. The Readiness for Transition Questionnaire (RTQ) survey was used in the study and was originally developed for transitioning AYA with kidney transplants. The survey is comprised of a Likert scale to ask questions regarding AYA autonomy and responsibility regarding his/her health care, the level of parental involvement in this care, and overall readiness for transition to the adult care facility. A response of a 1 indicated an answer of "not responsible at all" to a question, while a 4 indicated that the AYA was "almost always responsible" for the aforementioned task. AYA reported a range of health care responsibility from a 1.62 to 3.42, on the Likert scale.[8] Examples include calling in prescriptions and having monthly labs drawn.

When asked about parental involvement, AYA's answers ranged from 2.80-3.77, which demonstrates that they thought their parents were responsible for most of their health care behaviors.[8] In comparison, parents reported a range of 1.68-3.05 for AYA health care responsibility and indicated that they were often involved in most aspects of health care responsibility for AYA. The AYA' average reported readiness to transfer to adult care was 2.02 (somewhat ready), while the parents rating was 1.83 (not yet ready but approaching ready). AYA did not view parental involvement as an indicator of their readiness to transition.

According to the National Resource Directory hosted by the Centers for Disease Control and Prevention (CDC), as of March 2018, there are currently 235 SCD providers/treatment centers and 107 SCD Associations/Nonprofits/Foundations and/or Support Groups in the United States.[43] Of these treatment centers, 167 (71.1%) are pediatric care facilities, 44 (18.7%) are adult care facilities, 14 (6%) treat both children and adults, and 10 (4.3%) did not specify whether they treated children, adults, or both.[43] Seven states (14%) had neither a pediatric nor an adult treatment facility

for SCD and 15 states (30%) had a pediatric care facility listed, but either no adult care facility or an unspecified care facility listed.[43] The lack of adult care facilities is a major problem for transition across the United States.

2.3.4 Transition for SCD in Pittsburgh, PA

In Pennsylvania, there are a total of nine care facilities: 6 pediatric, 2 adult, and 1 pediatric/adult reported in the CDC directory as of 2017.[43] Based on where an individual with SCD is born with Pennsylvania, he/she will be referred to the sickle cell center in his/her region. There are also six SCD Associations/Nonprofits/Foundations in Pennsylvania.[43] In Pittsburgh, there is one pediatric care facility, one adult care facility, and one non-profit organization.

A lack of adult providers who have the expertise in and are available to treat adults with SCD is a major barrier for transition for many regions;[114] however, this is not the case in Pittsburgh. Children and young adults with SCD from western Pennsylvania are primarily treated at the Children's Hospital of Pittsburgh of UPMC (CHP) until they transition. Most of these AYA with SCD currently choose to transition to the UPMC Adult Sickle Cell Clinic. Both the pediatric and adult care facilities work with the local community-based organization (CBO), the Children's Sickle Foundation, Inc. (CSCF) to help transition AYA to the adult care facility. However, barriers to transition remain.

While all patients who are lost to follow up are considered "transferred" to the adult care facility approximately after their 22nd birthday, the age of transition for AYA who are active in the pediatric program varies upon transition readiness. The transition process typically begins around age 16 to 18 years old, with transfer to the adult program typically completed by 20 years of age. This age corresponds to when many are transitioning from high school to either college or

other career ambitions. After an AYA has been identified as a candidate for transition to the adult program within the next year, CHP works together with CSCF and the adult care team, as well as the patient and parent/guardians themselves, to make a transition plan.

While there has been a partnership between CSCF and both the pediatric and adult care facilities in Pittsburgh that has allowed them to develop and implement this transition program, there have been no outcome measures used to assess the effectiveness of the program itself. This study will allow transition readiness of AYA before and after participation in the program to be assessed.

The collaborative nature of this CBO and its function within the local community will be described. Hopefully, this will help other care facilities or CBOs who may be trying to implement similar partnerships or programs. Experiences regarding transition from both the pediatric and clinical teams, as well as the CBO staff, will help identify any barriers within the transition program or issues in communication. The overall goal is to help improve and standardize the transition experience for AYA with SCD, including future transitioning AYA within the Pittsburgh and surrounding communities.

3.0   MANUSCRIPT

3.0   INTRODUCTION

Sickle cell disease (SCD) refers to a group of hereditary blood disorders that affect the way the body produces hemoglobin. In SCD, the sickle hemoglobin inside the red blood cells (RBCs) can polymerize, which can damage both the sickle RBC and the vascular endothelium. This RBC sickling can cause a variety of complications, including organ damage, pain crises, and infection.[1] The prevalence of SCD in the United States is 1 in 365 in African Americans and is estimated to affect between 72,000 to 98,000 individuals in the US.[11] While primarily African Americans are affected in the US, they are not the only population at risk. The most common type of SCD is HbSS disease, followed by HbSC disease.[14] Other variants include HbS/β^+-Thalassemia, HbS/β^0-Thalaseemia, HbSE disease, HbSD disease, and HbSO disease.[19]

While SCD was first described by James Herrick in 1910[21] and research was ongoing throughout the twentieth century, SCD did not become an issue of public health priority until the 1970s.[3] With increased public awareness, the National Heart and Lung Institute (NHLI), now known as the National Heart, Lung, and Blood Institute (NHLBI), started funding sickle cell centers throughout the US.[33] Funding in the 1970s also allowed for important medical advancements in the treatment of SCD, such as newborn screening, pneumococcal vaccinations, and preventative penicillin therapy.[35] These advancements have allowed for early intervention and helped to improve both lifespan and quality of life for individuals with SCD.[9]

Management of SCD is both preventative and symptomatic. Because the sickle RBC circulates in the blood stream to every tissue, SCD affects many of the body's organ systems. Thus,

the disease can manifest itself in many different ways throughout the body. The NHLBI has created a resource for health care providers of specific management guidelines that help detail how to care for individuals with SCD.[1]

Despite initial support for SCD funding, funding for both medical research and multidisciplinary clinical care is currently quite limited. The last federal funding for SCD was the Sickle Cell Treatment Act, which was passed by Congress in 2004 and expired in 2009.[32] A lack of funding also affects the availability of transition programs and adult care facilities for AYA and adults with SCD. There are currently 235 formally recognized SCD care facilities in the US, but the vast majority of these facilities (71.1%) are pediatric care facilities.[43]

Transition can be defined as "the purposeful, planned movement of adolescents and young adults with chronic physical and medical conditions from child-centered to adult-oriented health-care systems." [100] Transition is an important step for individuals with SCD, but one fraught with difficulties. There is a need for transition care for AYA with SCD due to a marked increase in survival into adulthood since the 1980's.[5] The burden of mortality has shifted away from childhood to the AYA period.[5] Explanations for this acute increase in mortality are unclear, but likely include the biologic accumulation of disease burden that begins to manifest itself in the AYA period coupled with an unsuccessful transition from pediatric to adult care.[64] Inconsistent preventive and therapeutic care also contributes to poor outcomes in AYA with SCD.[71] This makes the need for an effective transition program even more important.

An increase in mortality in AYA with SCD has been reported in the literature.[5,69,70] Quinn et al[5] conducted a cohort study in 2010 that looked at the changes in the causes and timing of death in individuals with SCD and found that the burden of mortality had shifted to AYA. Patients in their cohort transferred to adult care at age 18. The highest incidence of death was for individuals

who were 15 years of age or older.[5] Since the last analysis of their cohort in 2002, seven individuals had died. 85.7% (6/7) of these individuals had transferred to adult care within the past two years. In deaths that occurred from 1991-2000 in this cohort, the median age of death was 3.1 years old.[5] In the deaths that occurred from 2001-2007, the median age of death had increased to 17.1 years old.[5] The most likely explanation for this dramatic shift in median age of death is the implementation of the newborn screen and preventive measures for invasive pneumococcal disease in children under the age of 3 years old, which would have shifted the burden of mortality from very young children to adults. However, it is striking that the shift in age moved only to the AYA age range rather than an older age. It is very possible that this is at least partially explained by an unsuccessful transition from pediatric to adult care or by inconsistent or less coordinated care in the adult medical arena that is leading to poor outcomes in AYA.[71]

AYA with SCD who are transitioning have also been found to utilize health care more often. In a retrospective longitudinal cohort study, Blinder et al[71] examined health care resource utilization and costs to patients with SCD, especially those who had recently transitioned. Medicaid data from five states was used for analysis. For each of the 3,208 patients in the study, ED visits, as well as outpatient and inpatient visits, and their associated costs, were estimated.[71] Approximately one fifth (20.4%) of patients were observed through their transition to adult care at 18 years of age. A subset of participants who were eligible for iron chelation therapy (ICT) (greater than 10 transfusions) were divided into two groups: 1) those who received ICT as a marker of appropriate medical care, and 2) those who did not receive ICT, despite its clinical indication as a marker of noncompliance or a lack of adequate access to knowledgeable care. The non-ICT group's quarterly health care cost averaged $6,762 pre-transition compared to $14,511 post-transition, while the ICT compliant group's cost averaged $11,050 pre-transition compared to

$12,966 post-transition.[71] An increase in ED visits was observed in both groups, which could potentially explain the increase in quarterly health care costs. Blinder et al[71] suggested that these increases could be caused by decreased follow-up and preventative care in AYA. This study's findings help to demonstrate the shift from preventative to symptomatic care that an AYA with SCD may experience after transitioning to adult care and the accompanying burden on the health care system.

While AYA with chronic health conditions can face similar barriers while transitioning to adult care,[105] AYA with SCD face a few unique barriers when transitioning from pediatric to adult care. Stollon et al[111] interviewed pediatric and adult care providers for individuals with SCD and found that health disparities were often a barrier to transition for AYA with SCD. These disparities included education level, access to health care, and poverty.[111] The health care providers interviewed reasoned that these factors competed with the transition process and often won out over transition. AYA with SCD are disproportionately affected by these sociodemographic factors. Similar differences have been found in transition support programs for African American and Hispanic AYA.[112,113] Other factors that have been found to affect the transition process for AYA with SCD include perceived readiness to transition and an older age (older than 21) at transition.[2,8]

The Children's Sickle Cell Foundation, Inc. (CSCF) is a local community-based organization that works with the pediatric sickle cell clinical team at the Children's Hospital of Pittsburgh of UPMC and the Adult Sickle Cell Program at UPMC to help transition AYA with SCD in the community. While CSCF's transition program has been in effect for five years, its effectiveness has not been assessed. This study will evaluate its effectiveness by assessing AYA readiness before and after their participation in the program. The study will also gather experiences

and opinions regarding transition from the individuals who are providing care and support to the AYA. The following are this study's specific aims:

1. To describe a community-based organization's (CBO) transition program.

2. To assess AYA's readiness to transition and to determine if AYA's transition readiness improves following participation in the CBO's transition program.

3. To assess AYA's experiences with the CBO's transition program and following transition to the adult medical program.

4. To elicit perspectives and experiences regarding transition from 1) CBO staff and volunteers, 2) the pediatric clinical team and 3) the adult clinical team.

The overall goal is to improve the transition experience and effectiveness for AYA in the Pittsburgh area.

3.1   METHODS

3.1.1   Introduction

This project was conducted in collaboration with the Sickle Cell Clinic at Children's Hospital of Pittsburgh of UPMC (CHP) and the Children's Sickle Cell Foundation, Inc. (CSCF). This study was conducted to assess the current transition program for individuals with SCD in Pittsburgh. The study was reviewed and approved by the University of Pittsburgh Institutional Review Board on March 19, 2018, IRB# PRO17110603 (See Appendix A).

3.1.2 Participant Selection and Recruitment: AYA Study Population

AYA who participated in CSCF's Transition Together program in summer 2017 were eligible for participation in this study. Participants were recruited from March 24th to May 8th, 2018 during routine CSCF events and home visits from CSCF staff and volunteers. These events were a part of CSCF's "Saturday SMASH – Stay Active, Motivated, Smart, and Healthy – Program." The SMASH program occurs every other Saturday and each event has a special focus on wellness. The event that took place during this study was a dental program, which helped educate individuals with SCD and their families about dental hygiene and provided them with a free dental screening and dental hygiene products. The AYA who participated in this study had either officially transferred their care to the UPMC Adult Sickle Cell Program or had been recommended to start the transition process but remained in the care of the pediatric facility. The two AYA who had not yet transitioned were told that they did not have to answer questions related to personal experiences with transition and adult care. All participants went through an informed consent process prior to filling out the survey measures. Participants were informed about the purpose of the study, the potential benefits of participating in the study (such as adding to knowledge about transition), and potential harms, which included discomfort regarding questions asked, for instance, and what participation would specifically entail (completing two surveys).

Four of the six participants filled out the post transition surveys during the Dental SMASH event and two participants completed the survey measures during routine CSCF home visit with the researcher and a CSCF staff member. These surveys were self-administered. After the informed consent process was complete and any questions were answered, the two surveys were distributed to the AYA to fill out on their own. The researcher remained nearby and accessible in order to

answer any questions that arose. Once the participant had finished, the surveys were collected by the researcher.

3.1.3 Participant Selection and Recruitment: SCD Health Care Professionals and CBO Staff/Volunteers

The primary researcher works for the Pediatric Sickle Cell Department and was therefore acquainted with the pediatric clinical team staff. These staff members were invited to participate in this study with an e-mail request from the researcher. The e-mail explained the aims of the study, outlined the time commitment involved in participation, and provided them with a copy of the verbal consent for the study, since the IRB waived written informed consent for this portion of the study (Appendix B). Staff members of the Pediatric Sickle Cell team helped the researcher identify members of the Adult SCD Clinical Team who might be interested in participating in the study. An e-mail introduction was made via a pediatric SCD care provider to the aforementioned adult team members. After this introduction, the researcher sent an e-mail explaining the aims of the study, outlining the time commitment, and included the verbal consent for the study. If there was interest in participating, an interview was scheduled with the responding health care professional at a mutually convenient time and location.

The researcher also works for the Children's Sickle Cell Foundation (CSCF). Staff and volunteers of CSCF were invited to participate in the interviews during a weekly staff meeting. At this meeting, the researcher outlined the purpose of the study, the estimated time commitment, and handed out copies of the verbal consent to allow them to decide if they wished to participate. All interviews of CSCF staff and volunteers took place during regular business hours, with permission of CSCF's Executive Director. The Founder of CSCF was also interviewed.

3.1.4   Data Collection Tools: AYA

Eligible AYA had completed surveys as part of the CSCF "Got Transition" program in 2017. Information from these surveys was collected for each participant, in order to compare pre and post transition readiness within and between subjects. This information was completely de-identified and no protected health information was collected. AYA who participated in the study were asked to complete two additional self-administered questionnaires during the study recruitment period. The first was a 10-question survey that asked open-ended questions (see Appendix C) regarding transition. The survey consisted of two parts; the first part asked questions related to transition in general and the AYA's personal experiences regarding transition, while the second section asked questions about their personal experience with the CSCF transition program. AYA participants were also asked to complete a questionnaire from Got Transition, which is a program of the National Alliance to Advance Adolescent Health.[6] (See Appendix C). The Got Transition survey asked questions related to the AYA's confidence regarding their utilization of health care and their comfort level with their own medical information. The Got Transition survey was also administered at the beginning of the transition program in 2017. This survey was used to determine a change in transition readiness.

After the AYA completed both surveys, the identity was coded and data was entered on a coded data collection sheet (see Appendix C). No personal identifiers were collected and each participant was assigned a numerical code as an identifier. The file that linked participants' names to their codes was stored on a secure UPMC server.

3.1.5 Analysis of AYA Survey Responses

Once the AYA had completed the Got Transition survey, his/her answers were recorded on the Data Collection Form (see Appendix C). The first two questions of the Got Transition survey used a Likert scale from 0-10 to assess self-care importance and confidence in the AYA. A score of 0 indicated low confidence or importance and a score of 10 indicated high confidence or importance. The next section, "My Health," asked seven questions. Answers were recorded on a three-point Likert scale (3 = Yes, I know this. 2 = I need to learn. 1 = Someone needs to do this … Who?). An index score for each participant was calculated by adding together their responses to these nine questions. A lower index score corresponds to lower confidence in the AYA's health care. Index scores pre- and post- the CSCF transition program were calculated and compared within subjects to determine if there was a change in readiness after participating in the program. The scores for each individual question were also looked at for each participant before and after their participation in the transition program, in order to determine if there were any particular areas of change that were important. The Wilcoxon signed-rank test for paired data, as well as a paired t-test, were performed using JMP Pro Version 13 for Mac.

The responses of the AYA to the survey regarding their experiences with the CSCF transition program were categorized by question. Descriptive statistics were calculated for the responses.

3.1.6 Interviews with SCD Health Care Professionals and CBO Staff/Volunteers

Interviews were conducted in-person. The interviews were comprised of open-ended questions related to the interviewees' own experiences with AYA transition in SCD and how this process could be improved. Detailed notes were taken during each interview and transcribed into Microsoft Word. Any personal identifiers in the interview transcripts were removed.

3.1.7 Thematic Analysis of Interview Data

Thematic analysis, a qualitative research method, was identified as the most appropriate form of data analysis for the interview data. Braun and Clarke[115] define thematic analysis as a way to recognize, examine, and report on patterns, or themes, in the data. There are two primary methods of performing thematic analysis, inductive and theoretical or deductive analysis.[115] The themes identified in inductive thematic analysis are closely related to the data, while those identified in theoretical analysis are motivated by the researcher's analytical interest in a particular research topic.[115] For this study, inductive thematic analysis was performed as a form of data-driven analysis.

After the completion of the first two interviews, transcripts were typed up into Word. These two transcripts were read carefully to help start to identify emerging codes within the data. A codebook was developed during this initial reading that identified 30 codes present in the data, relating to topics such as age, readiness, and maturity. Interviews were conducted over a one-month period and additional transcripts were added to the transcript document as additional interviews were completed. As each additional interview was transcribed, the transcript was read carefully and coded line-by-line to identify the codes present in the data, in alignment with the

initial codebook. After these initial codes were developed, the transcripts were color-coded based on potential groups of the aforementioned codes, such as "family support" or "logistical barriers to transition" and a corresponding key was developed. A total of 10 additional codes were identified.

Memo writing is a way for researchers to write freely about their thoughts during the coding process.[116] This process can help researchers identify themes, write about individual codes, and develop connections between codes.[116] During this study, memos were written after the color-coding of the data in order to make connections among the codes and to describe emerging themes.

3.2   RESULTS

3.2.1   Demographics of AYA Participants

A total of eight adolescents and young adults were eligible for participation in this study and six were consented and completed the post-transition survey measures. All eight eligible participants had previously completed the pre-transition survey measures at the start of the CSCF Got Transition Program. The average age of the participants was 23.2 years old with ages ranging from 18 to 28 years of age. Among the participants, 4 (66.7%) were male and 2 (33.3%) were female. Two of the six participants (33.3%) had not transitioned to adult care, while four of the six (66.7%) participants had already transitioned.

3.2.2 Demographics of Health Care Professionals and CBO Staff and Volunteers

A total of 12 health care professionals and CSCF Founder, staff, and volunteers were interviewed. Five health care professionals were from the Pediatric Sickle Cell Clinic (41.7%), two health care professionals were from the UPMC Adult Sickle Cell Program (16.7%), and five staff and volunteers were from the Children's Sickle Cell Foundation (41.7%).

3.2.3 Themes Identified in Interviews with Health Care Professionals and CBO Staff and Volunteers

Thematic analysis of the interview transcripts revealed five themes related to the topic of transition.

1. Parental Encouragement of Autonomy

Many participants mentioned the importance of a parent or guardian encouraging independence, or an overall state of autonomy or self-sufficiency, in an AYA to help aid him/her during the transition process. An adult care provider defined autonomy in the context of SCD transition for an AYA as "Learning responsibility for their own health care and learning their own disease." (P5) This independence can often be facilitated by an AYA's parent or guardian, even long before the formal medical transition process begins.

One CSCF staff member mentioned the role parents play in encouraging autonomy in the child from a young age:

> "From a parent perspective, you need to prepare them at birth. Starting routines and being consistent is important." (P8)

Another CSCF staff member explained the parent's role during transition:

"It's the responsibility of the parent to help the child transition, too." (P9)

One health care professional mentioned that while she wishes parents would redirect questions to the child during their clinic appointments, sometimes the parents have not encouraged this autonomy in the child, and this becomes apparent after the AYA has transitioned to adult care, as demonstrated by the following story she shared:

"I also think that early on in childhood, parents/guardians can redirect to the child and require them to answer questions about their own health, rather than the parent/guardian answering them for the child. I saw an AYA who transitioned to the adult clinic and when she checked in, she said 'Oh, I don't do paperwork; my mom does that [for me].'" (P5)

While encouraging autonomy from a young age can help make a smoother transition for the AYA, doing the opposite could have a deleterious effect. A CSCF staff member explained:

"When you're a child, your parent does a lot and if the parent doesn't teach you, you won't know how to advocate for yourself." (P9)

2. Negative Feelings of AYA Affecting Transition

Examples of negative feelings of AYA, as reported from the perspectives of the providers, that were discussed during the interviews included anxiety, fear, distress, or anger. These negative feelings can influence an AYA's attitudes and/or behaviors regarding transition. Fear and anxiety surrounding the transition process and transferring their care to the adult clinic were frequently mentioned by CSCF staff and health care professionals as barriers to transition. As one health care professional mentioned:

"[There is] anxiety about the new sickle team, new providers, new ED [emergency department], [and the] new hospital system." (P12)

Health care professionals cited AYA's familiarity with the pediatric program and their perceptions about adult care as a barrier to transition for AYA. As one participant remarked:

"Some of them fear of what they have heard or expect from transitioning and fear of the unknown. They have been with Children's since day one and their comfort with Children's gets in the way. They think the adult side will be cold and dark and damp but it's not." (P7)

One health care professional said that for some AYA the fear surrounding transition stems from a misconception that transitioning will lead to an early death. They explain:

"[Some AYA have] misconceptions that they'll die [when they transition]. They think this is because of the hospital but instead it's because of their disease progression." (P2)

3. Introduction/Presentation of Transition to AYA

How transition is introduced or presented to AYA by health care professionals can influence how the AYA perceive and approach the process of transition. The fear and anxiety surrounding transition could potentially be assuaged by presenting transition to AYA as a milestone to be celebrated. One health care professional explains a possible approach (or strategy):

"Shifting to celebration, making it a positive experience, like a graduation ceremony might help. If we make the last transition meeting like a party, that might help." (P1)

Some health care professionals already frame transition positively:

"I first congratulate them on the milestone or I point out how a concern that we are discussing [in clinic] may be more optimally cared for by the adult sickle cell team. I also spend time explaining features of the adult team that are positive." (P12)

A shift in framing transition as a goal rather than a requirement was also mentioned by a CSCF staff member as potential solution. They expand on this idea:

"We need to make it a goal. Now it's an ultimatum/inevitable – it's going to happen … We need to make it a choice to transition rather than them having to do it." (P7)

4. Variability Regarding AYA Readiness to Transition

Interviewees frequently mentioned that AYA readiness to transition varies and depends on where an AYA is in his/her life. Rather than name a specific age that was ideal for transition,

interviewees contextualized their response in light of specific factors that affected AYA readiness

to transition. As one health care professional expressed:

> "I think it's individualized though – some AYA are off to college and independent; others have more social support and still live at home." (P3)

This variability in readiness also depends on other factors, like maturity, autonomy, social

support, and disease progression. One participant explains some of the variables they consider:

> "I think there's a gray area [regarding] age. There are a lot of variables, like maturity, social support/situation, knowledge, medical status, and their ability to take on an adult role." (P4)

Another health care professional explains their reasoning behind choice of age to transition:

> "Twenty-one has been a good age, but I'd say between 18-21 years old, because sometimes kids don't seem ready at 18, in terms of maturity and coming to appointments on their own, etc. For some [AYA], they're ready at 18. It also depends on [how] medically stable they are." (P1)

5. Logistical Barriers to Transition

Logistical barriers are defined in the context of this study as impediments to transition that

are related to the planning, management, or organization of the transition process. Identified

barriers included transportation, childcare, insurance, finding a primary care provider (PCP), and

locating the new adult care facilities, including Emergency Rooms.

One CSCF staff member discussed several logistic barriers an AYA may face:

> "The major challenge is transportation, like not having a car; that may be overlooked. Changing hospitals and providers and emergency rooms [could be] a challenge. Lots of providers are changing at this time and so is insurance." (P10)

One health care professional mentioned logistical barriers specifically as a risk factor for

an unsuccessful transition:

> "Logistics – transport, finding providers, insurance changes." (P3)

Insurance can become an issue for AYA who transition from pediatric to adult care in Pittsburgh. There are two major health care systems within Pittsburgh, University of Pittsburgh Medical Center (UPMC) and Allegheny Health Network (AHN). Currently the Children's Hospital of Pittsburgh has contracts with both UPMC and AHN. But when an AYA starts seeing an adult care provider for his/her SCD, there can be complications. Both UPMC and AHN employ hematologists, but only UPMC has dedicated hematologists for individuals with SCD. Sometimes an AYA's health insurance will cover visits with an AHN hematologist, but not with UPMC's hematologist at the Adult Sickle Cell Clinic.

> One health professional explains:

> "Insurance can also be a problem. There's only one pediatric provider in Pittsburgh, but AHN has hematologists so insurance sees this and won't cover going to the UPMC [for the adult clinic]." (P2)

> This participant relayed an anecdote about an AYA who was turning 22 and therefore must

transition to the adult care facility. This individual has insurance under her mother, and it will not cover her visits to the UPMC Adult Sickle Cell Clinic. At the time the participant told this story, the mother was attempting to find a different job that would cover these visits through employer-sponsored insurance. The participant explained that this was the mother's only option to help her daughter have insurance coverage, or else her daughter would have to take out her own health insurance. (P2)

> Another participant said that the Pediatric Sickle Cell Team was unaware of the insurance

issues, like the one mentioned above, until a few years ago. They explain:

> "Insurance – we didn't know it was a problem for AYA initially. We can work with families in advance now since we know. Mentioning [transition] when the AYA is 18 years old gives us three years to work on it." (P1)

The Pediatric Sickle Cell Team helps the AYA navigate insurance should insurance coverage change when the AYA transitions to adult care. One participant explains:

"[The pediatric] social worker calls the new insurance company with the AYA and sits with him/her while the AYA talks on the phone to the insurance company." (P2)

Another logistical barrier that was identified was the ability of the AYA to locate the new provider. As a solution to this, as well as to provide support to the transitioning AYA, a member of the pediatric sickle cell team offers to accompany the AYA to the adult program during his/her first appointment:

"We meet the [transitioning AYA] at their first appointment [on the adult side]." (P2)

Other logistical barriers include access to childcare and having a PCP. As one participant explains:

"No childcare is available on the adult side if the AYA has young children. The adult side likes patients to have a PCP but they don't [usually] have one and use their hematologist as one instead." (P1)

The Pediatric Sickle Cell Team has recently partnered with the Adolescent Medicine clinical team at the Children's Hospital of Pittsburgh of UPMC. The doctors in this clinic can act as the AYA's primary care physician through the age of 28 years old; they also provide additional support for transition skills and other non-SCD-related health concerns the AYA may be facing during this period of time. Regarding the need for childcare at the adult care facility, no solution was readily identified during the interviews.

3.2.4 AYA Survey Results

Got Transition Survey

Approximately 83% (5/6) of AYA participants completed the entire Got Transition survey both before and after participation in the CSCF "Got Transition" program. One participant did not complete the first two questions of the Got Transition survey in summer 2017. This participant was included in the data analysis for questions they did complete, but not included in the data analysis of pre- and post-transition index scores (Table 1) because a complete index score could not be calculated with the missing data. Index scores for the remaining five participants were calculated. There were a total of 47 points possible for the overall index score. Participants' index scores ranged from 29 to 46 before participation in the transition program and from 37 to 44 after participation in the CSCF Got Transition program. The mean index scores for pre- and post-transition were 39.4 and 41.6, respectively.

Two participants' (40%) index scores were lower after participation in the CSCF Got Transition program, each by a total of two points. Three participants (60%) had an increase in index score after participation in the Got Transition Program. Two of the three had increases of 2 points each, while the other participant showed an increase of 11 points post-transition program. Using a Wilcoxon signed-rank test, no statistically significant change was found (p-value = .7500) between pre-and post-transition program index scores. Of note, the results of a paired-T test were also not statistically significant.

The Wilcoxon signed-rank test was also performed for each of the four questions of the survey that had an observable change before and after participation in the transition program. No statistically significant changes were found for these four questions (Table 2).

Table 1: Index Scores of Participants

Participant	Index Scores before Participating in CSCF Transition Program	Index Scores after Participating in CSCF Transition Program	Difference in Scores
#1	46	44	-2
#2	39	37	-2
#3	41	43	+2
#4	29	40	+11
#5	42	44	+2

Table 2: Wilcoxon-Signed Rank Test Results for Individual Questions

Question	Mean Before Program	Mean after Program	N	P value
Index Score	39.4	41.6	5	0.7500
1	7	7.8	5	0.5122
2	5.4	6.8	5	0.3383
8	2.83	3	6	0.3632
9	2.83	3	6	0.3632

AYA CBO Experiences Survey

Age of Transition

The AYA participants were asked at what age an individual with SCD should transition to adult care. 50% (3/6) of participants stated that transition should occur at age 21. Other participants responded with the ages 17, 14-15, and 23. When asked to explain his/her choice of age, some individuals used their own personal experience with transition to make this decision. One participant chose age 21, as he explains: "because I wasn't ready [when I transitioned]." (P3) Another participant selected age 23 because this was the age at which he transitioned: "It's when I transitioned and I think it's a good age." (P6)

One individual mentioned an adolescent's emerging independence as a factor affecting which age he chose. He explains: "I feel that [14-15 years old] a good age to transition because you're at that [age] where you're having a voice of your own and you should learn early how to do everything." (P2)

Challenges Faced While Transitioning

When the transitioned AYA were asked what their biggest challenge was regarding transitioning to adult care, two mentioned logistical issues. Their challenges included "Different doctors and learning the new hospital" (P6) and "Getting around from place to place." (P5) One participant was anxious about the care she would be receiving at the adult facility: "Paranoia that the doctors wouldn't be as prepared" (P4) and another mentioned "time" was his biggest challenge when transitioning. (P3)

Differences between Pediatric and Adult Care

Of the four who had transitioned to adult care, three mentioned differences in the atmosphere and availability of things to do in the adult facility. Two of the three mentioned availability of entertainment. One said the biggest difference for him was "Video games at Children's/no video games at adult hospital." (P6) Another said the biggest change for him was "Just the difference in atmosphere and entertainment." (P5) One participant remarked on the comforting environment of the Children's hospital and the difference she felt when admitted in the adult hospital. She remarks:

> "[There are] fewer colors and nothing for anyone to do. All you can do for fun is walk up and down the hallway. All you can do is be in your room, watch TV, and wait. Why isn't there something to do for people who are well enough? It's so important for kids to have a happy environment, but it's not for other ages – why not?" (P4)

This participant also stated that she felt she received more care at the Children's hospital.

Improvements to Transition:

Three of the six survey participants provided suggestions for improvements to the transition process in Pittsburgh. They included meeting with the adult doctor before transitioning, providing transportation for sickle cell patients, and "talking and [doctors] writing things down." (P6)

Improvements to CSCF Got Transition Program

When asked how CSCF could improve their Got Transition program, one responded, "It is fine the way it is" (P2) and one did not respond to the question. Better transportation was included to help improve the program. Another participant suggested a more formal schedule for the program. He said: "Make scheduled plans and stick to them." (P5) One participant mentioned that

"in depth-discussion and home visits are nice" (P4) and suggested these as an addition to the current transition program.

3.2.5 CSCF's History and Formation

An interview was also conducted with CSCF's Founder to lay the foundation for the development of their Transition Together program within the context of their larger sickle cell community mission. This section will provide an excerpt of this interview which explains why the Foundation was created and the Founder's original goals when establishing the Foundation:

> "When my son was born in 2000, I found out that he has sickle cell disease via the newborn screen. I had a great social worker who told me that how you cope with this disease is how he will. He was in and out of the hospital as a child and I felt like I needed to do something. I wanted to meet some other parents who were going through the same thing I was. One morning, I woke up with a question, "What if?" "What if there was an organization that met the needs of children with SCD and their families, so that no one would have to walk in my shoes?" [CSCF] has changed the course of SCD in Pennsylvania, changed lives … and raised the ceiling for what kids with SCD can do."

3.2.6 Overview of CSCF

Founded in 2002, CSCF is a community-based organization located in Pittsburgh, PA that helps children and families affected by SCD.[117] Its goal is to impact positively the lives of children and families with SCD in the community. CSCF provides support in a variety of ways. CSCF serves as a source of financial, educational, and family support for its families throughout the community. CSCF provides educational support to families by meeting with school staff, such as nurses or teachers, to educate them about SCD, attends Individualized Education Plan meetings to

advocate on behalf of the child, and retrieves homework for children who are absent from school because of their illness.

Throughout the year, CSCF hosts various activities, including Back2School Bash, where the child and his/her siblings are given backpacks with school supplies to help them prepare for the school year ahead. CSCF also hosts a range of family support programs, including a bi-monthly SMASH (Stay Active, Motivated, Smart, and Healthy) initiative where families and children with SCD meet to play games and socialize with other families who have been affected by SCD. They also have a personalized "Got Transition" Program to help AYA make the transition from pediatric to adult care. CSCF collaborates with the Children's Hospital of UPMC Sickle Cell Program and the UPMC Adult Sickle Cell Program.

3.2.7   CSCF's Transition Program

This section will include an explanation of how CSCF's transition program was developed and what the program specifically entails.

3.2.7.1 Emerging Need for a Transition Program

Although CSCF was established in 2002, its transition program was not created for another eight years. The need for a transition program was identified as the CSCF program evolved, as described by CSCF's Founder:

> "We've created a systematic way to help navigate very challenging times in life. The transition program started in 2010-2011 – we noticed that kids were getting older and heard about the higher mortality rates in this age range, and I thought 'maybe we need to prepare them for this big old thing called transition.'"

3.2.7.2 Development and Evolution of the CSCF Transition Program

CSCF's Founder describes the first transition program:

"When it first started we had group transition sessions, twice a year, once in the winter, once in the spring, that lasted 4-6 weeks. The goal was to give each AYA individualized time too. Now CSCF has the benefit of the Got Transition resources. Back then we had to develop it from scratch. We taught them about voting, finances, etc. versus just medical information. … we also had kids and sibs come too."

3.2.7.3 Current Transition Program

Twice a year, CSCF facilitates a transition program called "Got Transition," which works

to assess AYA's skills regarding their own health management and identify any gaps in

knowledge.[118] The program also works with the AYA to develop a plan to help them reach future

goals; examples include applying for jobs through the Office of Vocational Rehab (OVR) or

applying for a learner's drivers permit.[118] The "Got Transition" program is tailored to each

individual and can occur before or after an AYA is transferred to the adult care facility.[118] Ideally

transition occurs before transfer, because this also gives the AYA a chance to acquire new skills

that may have been lacking prior to their transfer of care. The aim of the CSCF transition

program is to increase AYA's knowledge of SCD and to help them acquire the necessary life

skills they need to thrive in adulthood.[118]

CSCF's Executive Director describes the process of their transition program:

"First is a welcome/congratulations that they've been recommended to transition. Next is our investigative phase – focusing on supports and goals they have and finding those out. For instance, if they want to get into school, we help them academically. Or if they want to move out from home, we give them options to help them think through it. We give them a realistic viewpoint of their situation and try to complement the positives and negate the negatives. After that, we locate support services in the identified areas. Next, we monitor their progress and check in with them. This last part is continuous – we also help them through their adult years as well."

3.3   DISCUSSION

This study is the first to evaluate both CSCF's transition program and a community-based organization's transition program. While previous research has explored AYA's perspectives about transition specifically in Pittsburgh[119], no research has been conducted that elicits perspectives from the AYA's care providers and CBO staff and volunteers or from those who specifically completed a CBO-based transition program.

The five themes identified from the thematic analysis of the interview transcripts have previously been documented in the literature published about SCD transition and AYA. Porter et al[120] found that some AYA reported having parents who encouraged their autonomy, emphasizing advocating for themselves and having the ability to communicate their own needs. This need for parental encouragement of autonomy was echoed in the current study by CBO staff and health care professionals. Stollon et al[111] interviewed 13 pediatric and adult care providers regarding AYA transition and potential barriers. Encouraging self-management and independence regarding the AYA's health care were both cited as positive ways to help prepare AYA for transition.[111] Based on the results of the current study and what is published in the literature, AYA and health care providers both felt that AYA independence regarding their own health care was important for a successful transition to adult care. Encouraging independence was frequently mentioned by health care professionals and CBO staff as a way to help prepare AYA for the transfer of their care and to help them advocate for themselves in the future.

While AYA have reported that negative interactions with adult health care providers affected their transition experience in previous studies,[73,120] such interactions were not identified as a barrier to transition by AYA, CSCF staff, or health care providers in the current study. Overall, the perception of negative feelings such as anxiety in the AYA were reported by health care

professionals and CBO staff in the current study as factors that hindered the transition process. Health care professionals reported that AYA expressed a "fear of the unknown" and were described as anxious regarding their transfer because of their comfort level with the pediatric care facility. A novel finding from the provider and staff interviews was that some AYA have a misconception about the adult care facility and associate it with death, mistaking adult care as the reason behind the increased mortality in AYA, instead of the progression of their disease being to blame.

In addition to negative feelings of AYA affecting the transition process, the way that transition is framed by health care professionals can also have an impact on how AYA view transition. In the current study, health care professionals and CSCF staff suggested that the way transition is presented to AYA could be improved. Health care professionals suggested trying to change transition from an obligatory task to a positive accomplishment of the AYA. Of note, this is something that CSCF is already doing during their transition program. CSCF's Executive Director mentioned that when an AYA is recommended for enrollment in the CSF transition program, they are congratulated on this accomplishment. This could potentially lessen some of the fear and anxiety that some AYA have surrounding transition, by making it an achievement rather than a punishment. This sentiment was also observed in the literature. For instance, Treadwell at al[121] mentioned that the AYA "graduate" from their transition program and are given a gift and a certificate affirming their graduation. This is consistent with a positive framing of transition as an "accomplishment," rather than something that is "inevitable."[120]

Regardless of how transition is framed, health care professionals and CBO staff agreed that transition readiness varies for each AYA. Participants thought that readiness should be determined by a variety of factors such as maturity, knowledge of disease, social support, disease progression,

and independence. Much of the literature on AYA transition readiness in SCD focuses on parental and patient perspectives. Porter et al[120] found that AYA thought that transition should not occur at a specific age, but rather a range of ages (18-25 years old), depending on an individual's readiness to transition, which is consistent with this study's interview data of provider and CBO staff perspectives, as well as the survey data that inquired about age at transition.

Logistical barriers related to the management, planning, or organization of the transition process were mentioned as obstacles to transition in the current study. These logistical barriers included insurance, transportation, and childcare. Regarding insurance, McPherson et al[7] found that AYA were concerned about what their insurance would cover when they moved to the adult care facility. One health care professional mentioned that the health care providers were unaware that insurance was an issue during the transition process until an AYA mentioned it to them. Now the pediatric team mentions transition to AYA starting at age 18, which gives them two to three years to solve any logistical issues relating to insurance coverage.

In addition to insurance, transportation was identified as an important barrier to transition in the current study. Andemariam et al[2] found that there was a need to increase access to their adult SCD center after observing that geographical distance from an AYA's care facility was a risk factor for an unsuccessful transition. As a result of their study, the adult clinic's social worker now explicitly discusses transportation with patients before they transition to adult care.[2] If transportation is needed, clinic staff will help the patient explore transportation assistance or other resources to help the patient attend the clinic.[2] In Pittsburgh, gas cards and bus tickets are currently distributed to families in need of transportation assistance. Currently, CSCF gives their transition program participants weekly bus passes for the duration of the program to help them learn how to navigate public transportation in Pittsburgh.

A novel logistical barrier that was identified is access to childcare in the adult clinic. While attending appointment at the Children's Hospital of Pittsburgh of UPMC, childcare is provided. At the UPMC Adult Sickle Cell Clinic, childcare is not provided. If an AYA has children, this means that he/she must find appropriate childcare in order to attend his/her clinic appointments, which can put additional social, emotional and financial burdens on the AYA, perhaps making them less likely to attend clinic appointments.

A crossover clinic between the pediatric and adult programs was also mentioned during several health care professional interviews as a potential solution to the AYA's discomfort and anxiety regarding the adult facility. The idea behind the clinic is that the adult physicians or other health care providers would visit the Pediatric Sickle Cell Clinic. This would allow the AYA to meet the new clinical team in a comfortable and familiar environment, perhaps assuaging some of the AYA' negative feelings about moving to the adult facility.

CSCF has recently started a peer navigation program that is designed to engage AYA who are about to or have recently transitioned and to stay involved with CSCF. CSCF received a grant that allows them to employ a group of AYA to help with CSCF's programming. The AYA attend trainings and then work at events that CSCF runs. For example, during the Dental SMASH event, the peer navigators demonstrated the proper tooth-brushing technique to attendees of the program and interacted with the families who attended the event. The goal of this peer facilitator program is to provide the AYA with new responsibilities, to encourage them to be involved in their community, and to serve as role models for the younger kids at CSCF. Regarding specific changes to the CSCF transition program, one AYA mentioned a more defined schedule would be beneficial and another mentioned that transportation assistance would be helpful.

Regarding AYA transition readiness, the average pre-test score was 39.4 out of 47. This pre-transition program score is already reasonably high. This could signify that, while the transition program did not statistically change the transition readiness score, the AYA already had knowledge and confidence within the tested areas and that they were already fairly well-prepared for transition. An improvement in overall readiness was observed before and after participation in the CSCF transition program, with a mean index score of 41.6 post-participation in the program. While a statistically significant change was not seen, if the AYA were already reasonably well-prepared, then this score might not be expected to change dramatically.

For the questions for which Wilcoxon-signed rank tests were performed, the mean scores before participation in the program were as follows: 7.0/10.0, 5.4/10.0, 2.83/3.0, and 2.83/3.0. The mean scores after participation in the program were 7.8/10.0, 6.8/10.0, 3.0/3.0, and 3.0/3.0, respectively. The lowest average score was a 6.8 post-participation in the transition program. This question this average corresponded to asked about the AYA's confidence regarding their self-management of their own health care. This could be an area of improvement for future transition programs.

As previously mentioned, five of the nine questions did not see an observable change in mean score, but this was because the AYA reported that they already knew the answers to the questions, thus scoring the maximum total of 3.0 out of 3.0 possible points for the index scores both before and after the transition program. These questions included: the AYA knowing their own medical needs, being able to explain their medical needs to others, knowing their symptoms and when they should see a doctor, knowing what to do in a medical emergency, and knowing their medications and when to take them. This shows that the AYA already reported a good understanding of these specific transition skills even before starting the CSCF transition program.

This aligns with what the health care professionals and CBO staff mentioned when interviewed; AYA readiness to transition was frequently associated with improved medical management and knowledge of their disease.

3.3.1   Study Limitations

The results of the AYA surveys are limited in their generalizability to other AYA with SCD, since they are based on a small sample of AYA (5-6). This data was also limited by the selected survey measures. By choosing an open-ended, self-administered survey as one of the methods of data collection, the amount of data collected was limited by participant interest and motivation. Several participants left questions blank, which limited the researcher's ability to interpret fully all of the data collected. One participant seemed to misinterpret most of the questions on the CSCF survey questionnaire, as they mentioned doctors in a few of their answers, rather than CBO staff, when no doctors were involved in the CSCF Got Transition program. This suggests there is possibly a need to be more explicit in the verbal instructions on the researcher's part, or a need for clearer, more easily understood questions on the survey. More clarity during the transition program itself could have cleared up this confusion if participants thought that doctors were involved in the program when they were not. A more informative source of data collection for this aim could be an in-depth interview. Similar questions could be explored, but this would allow for clarifications to be made along the way and for a more robust set of data regarding AYA experiences with transition and the CSCF Got Transition program to be collected and analyzed. However, recruitment of the AYA was difficult during this study and participant interest in interviews appeared limited. Group interviews with the AYA could be a solution to this, as they may be more likely to participate in the interviews if they know their peers are also participating.

Interviews with AYA would also allow more direct comparisons to be made between what the health care professionals and CBO staff discussed and what AYA discussed. Because two different methods of data collection were used, while some comparisons could be made, the ability to do so was limited.

The Got Transition survey method provided a method of data collection that was easy to follow for AYA and personalize for various chronic health conditions. A limitation of this data was its limited scope. This survey focused on an AYA's knowledge regarding his/her health and autonomy regarding transition. Other data, regarding logistical barriers to transition, for instance, could have been beneficial to interpret in light of the interview data.

3.3.2   Future Research

While no statistically significant difference was found between the pre- and post- scores for Got Transition readiness survey for the six AYA who participated in this study, the results provide a foundation that can be built upon for future studies. For example, transition readiness surveys from a younger age group could be collected in order to compare their readiness to the older AYA. This could help identify needs for programs that could help address any deficiencies in knowledge in the younger age group that CSCF could pilot or incorporate into their Saturday SMASH programming. Another future research direction includes collecting survey data from more AYA as they transition their care. This would improve the power of the preliminary data of this project, which could lead to significant changes being observed in the larger data set.

The identification of the strengths and weaknesses of the CSCF Got Transition program can be used to direct the development and improvement of future CSCF transition programs. Suggestions for improvement from the AYA surveyed included more home visits from CSCF,

providing transportation to and from the transition program, and having a more consistent schedule for the program. The themes identified in the thematic analysis can help inform both CSCF regarding their transition program and also the pediatric and adult sickle cell programs in Pittsburgh, as they work to develop a standardized transition process.

3.4   CONCLUSION

This study was the first to evaluate formally the CSCF Got Transition Program. We found that the AYA who participated in this program already had good composite scores from the transition readiness survey prior to the CBO transition program with no significant change following completion of the program. The data collected from AYA (N=6) regarding their personal experiences with transition and the CSCF Got Transition program can help CSCF implement changes to this program. The interview data from interviews with CBO staff/volunteers and health care professionals (N=12) identified five themes: Parental Encouragement of Autonomy, Negative Feelings of AYA Affecting Transition, Introduction/Presentation of Transition to AYA, Variability Regarding AYA Readiness to Transition, and Logistical Barriers to Transition. Identification of these themes can help the pediatric and adult care facilities in Pittsburgh develop a more formal transition program, which has been recognized as a need within the SCD health care community.

4.0   RESEARCH SIGNIFICANCE TO GENETIC COUNSELING AND PUBLIC HEALTH

There are 10 essential public health services that fall under the three core functions of public health. The core functions of public health include assessment, assurance, and policy development.[122] The current study covers each of these three core elements. Assessment was employed by investigating the health problems for AYA with SCD, specifically around the time of transition. Assurance includes evaluating the effectiveness, quality, and accessibility of health services. This study incorporated assurance by evaluating CSCF's transition program and transition care in Pittsburgh. The third core function of public health is policy development. This study evaluated CSCF's transition program and interviewed CBO staff and health care providers to help develop a more formalized transition program that will support the AYA with SCD in the community.

Regarding policy implementation, a need for a more formalized transition program for SCD both within the city of Pittsburgh and across the US was frequently mentioned when conducting the study interviews. The Pediatric Sickle Cell Team is working to pilot a transition guide that AYA can use as a resource while they transition. This guide covers areas such as medications, insurance, psychological resources, and transportation. Genetic counseling could also be beneficial to AYA who are transitioning, to help them fully understand the reproductive outcomes and the importance of knowing their partner's sickle cell trait status. This would allow the AYA to make fully informed decisions and better prepare for their pregnancy.

The current study could also be used a resource for genetic counselors who see patients with SCD but who do not have local resources available to them, such as hematologists with expertise in SCD or an established SCD program. This study can help genetic counselors understand the challenges that AYA with SCD face before and after they transition their care. A genetic counselor's awareness of these difficulties could allow him/her to identify potential resources for the patient before the counseling session. These resources could include the Got Transition resources, information about community-based organizations or support groups, or logistical resources, such as transportation vouchers.

An awareness of these problems could also allow the genetic counselor to think of questions to ask the AYA during the session, such as "Do you have an adult hematologist?" "Do you have a PCP?" or more psychosocially-focused questions such as, "What kinds of social support do you have at home?" All of these questions could help the genetic counselor assess the AYA's readiness to transition and allow him/her make referrals to other health care providers or organizations.

5.0   PUBLIC HEALTH ESSAY

5.1   BACKGROUND

Overview of SCD

Sickle cell disease (SCD) refers to a group of inherited blood disorders that affect how hemoglobin is made in the body. Sickle hemoglobin can polymerize inside the red blood cells (RBC), which can damage both the sickle RBC and the vascular endothelium. The sickling of the RBCs can cause complications such as pain crises, organ damage, and infections.[1] Sickle cell disease is estimated to affect between 72,000 to 98,000 individuals in the United States.[11] In the US, SCD primarily affects African Americans, but they are not the only population at risk. SCD can occur in any racial group, but appears most commonly in individuals from Central and South America, Africa, and in people of Indian, Middle Eastern, Asian, and Mediterranean descent.[12] Each year, an estimated 300,000 newborns are born with SCD worldwide.[13] SCD is also the most common genetic condition that is caused by a single gene mutation.[14] The most common type of SCD is HbSS disease (64% of hemoglobinopathies worldwide), followed by HbSC disease (16.1% of hemoglobinopathies worldwide).[14] Other variants include HbS/β^+-Thalassemia (HbS/ β^+-Thal) HbS/β^0-Thalassemia (HbS/β^0-Thal), HbSE disease, HbSD disease, and HbSO disease.[19]

Overall, HbSS disease and HbS/β^0-Thal are the most severe forms of SCD.[123] The total amount of Hemoglobin S in the red blood cells is the main determinant of disease severity in SCD.[123] This fraction is highest in HbSS disease and HbS/β^0-Thal, and lower in other milder genotypes such as HbSC disease and HbS/β^+-Thal.[123] At a molecular level, HbSS disease is caused by two homozygous mutations for the Glu6Val mutation in the *HBB* gene. Beta thalassemia occurs

when the β-globin chains are reduced or completely absent due to mutations in the *HBB* gene. These can be co-inherited with HbS, which results in sickle cell-beta thalessemias. Sickle cell-beta thalessemias are typically classified as either HbS/β^0-Thal or HbS/β^+-Thal. The genotype HbS/β^0-Thal has a mutation in *HBB* that prevents any adult hemoglobin (HbA) from being made.[19] Because of the absence of HbA, HbS/β^0-Thal often has similar, more severe, clinical manifestations to HbSS disease.[19] The Cooperative Study of Sickle Cell Disease data looked at the incidence of SCD complications and found that an acute painful episode (pain crisis) occurred at an incidence rate of 80 per 100 patient-years for individuals with HbSS disease and 100 per 100 patient-years for those with HbS/β^0-Thal. For individuals with HbSC disease and HbS/β^+-Thal, the incidence rates for a pain crisis were each 4.0 per 100 patient-years.[123]

SCD, Emergency Department (ED) Visits, and Cost

Individuals with SCD are more likely to require ED care, even with regular clinical follow up and preventive measures, in comparison to other individuals with chronic diseases.[124–126] Lanzkron et al[124] used the National Emergency Department sample (NEDS) for 2006 to estimate ED use for individuals with SCD in the United States. The NEDS is sponsored by the Agency for Healthcare Research and Quality and contains data from 950 hospitals across the country. It also approximates a stratified sample of ED visits across 24 states. Using ICD 9 codes for SCD, Lanzkron et al[38] identified a total of 50,418 ED visits in the NEDS sample. From this, they estimated the national amount of ED visits for SCD in 2006, which was 232,381. Of these 232,381 visits, there were 188,194 ED visits for adults (18 years and older) with SCD and 44,188 ED visits for pediatric patients with SCD (under age 18). 68% of patients were identified to have HbSS disease from the ICD 9 codes, 2% were coded as HbSC disease, 2% had sickle cell-beta

thalassemia, and 28% were coded as having an "other" diagnosis of SCD. The researchers also estimated the total charges for all SCD-related ED visits for 2006, which were $356 million. When hospital admissions from ED visits were added to this number, the overall estimated cost was $2.4 billion for 2006.

Lanzkron et al[124] also calculated the average hospital admission rate per 100 patients annually, as well as annual visit costs per 100 patients, both calculated using admission and cost data from 2006. These values for SCD patients were compared to those with other common chronic diseases, including congestive heart failure (CHF) (prevalence in US: 4.8 million), asthma (34 million), and HIV (1.1 million). The study used an estimated prevalence of 100,000 for SCD. Individuals with SCD had an average annual admit rate of 68.4 per 100 individuals, compared to rates of 17.3 per 100 for individuals with CHF, 1.1 per 100 for individuals with asthma, and 5.1 per 100 individuals with a diagnosis of HIV. When comparing the average cost per 100 patients in each of these four groups, SCD had the highest overall expenditures. The average annual cost per patient was $15,000 for SCD, $5,000 for CHF, $144.11 for asthma, and $2,818.18 for HIV. The difference in these costs was caused by a higher overall frequency of ED visits for individuals with SCD and not by a higher average cost of hospitalizations for these individuals.[124] This study helps demonstrate that individuals with SCD have an increased utilization of EDs and the estimated expenditures that are associated with these visits and subsequent hospitalizations.

Other studies have compared the ED visit rates of individuals with SCD to other individuals who have similar demographics but do not have a diagnosis of SCD. Shankar et al[127] examined the health care utilization in children and adults with SCD who were enrolled in TennCare, Tennessee's Medicaid-managed health care program. In order to be included in the study, patients had to be enrolled in TennCare at any point in time from January 1995 to December 2002.

Administrative claims and information from health care encounters were the primary source of data for this study. Participants were determined to have SCD if they had a hospitalization with a discharge diagnosis of SCD or had two outpatient visits, which could include ED, clinic visits, or 23-hour hospital visits, and these two visits had to be at least thirty days apart with a coded diagnosis of SCD. A total of 2,102 patients were included in the final data analysis. Data collected within the cohort was also compared to a random sample of 10% of the African American population who was also enrolled in TennCare during the study's time frame but did not have a diagnosis of SCD. Individuals with SCD were found to have a 2-6 times higher rate of ED visits compared to the non-SCD African American population that was used for comparison (P < 0.001). This study shows that individuals with SCD utilize the ED more frequently than individuals without a diagnosis of SCD.

Pain crises are the most common reason for individuals with SCD to present at the ED.[61] As the sickle red blood cells are traveling through the blood vessels, the RBCs can polymerize which can block blood flow. This causes pain that can have a sudden onset and can range in severity and duration.[61] Several studies have used medical codes to identify the specific reasons that individuals with SCD are admitted to the ED. For example, Yusuf et al[126] used data from the National Hospital Ambulatory Medical Care Survey (NHAMCS) to estimate the national frequency of ED visits for individuals with SCD for the years 1999-2007. SCD-related ED visits were identified from ICD 9 codes. Between 1999-2007, it was estimated that approximately 197,333 SCD-related ED visits occurred per year. In this study, approximately 78% of the patients' ICD 9 codes cited pain as the primary reason for the visit. A limitation of this study is that it did not identify pain crises specifically within the diagnosis codes. In a previously mentioned study by Lanzkron et al,[124] 73.7% of adults and 54% of children had diagnosis codes indicating that a

pain crisis was the primary symptom for presentation to the ED. Other codes included asthma (6.6%), pneumonia (5.2%), acute chest syndrome (2.3%), and stroke (0.27%).[124] These studies help quantify how often pain crises are the most frequent cause of ED visits for individuals with SCD.

The high health care expenditures - an estimated $2.4 billion dollars[124] in 2006 – for ED visits and related hospitalizations for individuals with SCD place a burden on the US health care system. By reducing the number and severity of pain crises that individuals with SCD experience, these costs could possibly be reduced. One potential solution for a subgroup of individuals with SCD is optimizing the use of and compliance with the medication hydroxyurea (HU). HU is the only FDA approved drug that is widely available in the US proven to reduce the pain rate and ED/hospital utilization rate for individuals with SCD.[74]

Hydroxyurea and Recommendations for Use

HU is recommended for all individuals with HbSS disease and HbS/β^0-Thal.[1] HU works by increasing the amount of fetal hemoglobin (HbF) in the red blood cells, which makes them less likely to sickle, due to the increased amount of oxygen that is present.[76] Higher levels of HbF are associated with reduced disease severity in SCD.[123] Hydroxyurea was initially only approved for adults with SCD and moderate to severe pain crises, but as of December 21, 2017, the FDA has approved hydroxyurea for use in pediatric patients with SCD.[78] There is limited data available for the efficacy of HU in individuals with milder genotypes.[128] Most of the literature on HU refers to individuals who have HbSS disease or HbS/β^0-Thal. This is due the fact that fewer individuals with milder genotypes have severe complications from their SCD, and were therefore excluded from the initial HU clinical trials.[128] However, HU is now also commonly being used in individuals

with other sickle cell genotypes who are experiencing increased pain or other complications of SCD.[129]

Utilization of HU in the SCD Population

The clinical trial that demonstrated the efficacy of HU was a double-blind, randomized study that included 299 participants (51.5% female, 49.5% male,) at 21 clinical sites throughout the United States.[74] Eligible participants were between the ages of 18 and 50, who had been hospitalized or visited the ED at least three times in year prior for an acute pain episode related to SCD. [75] Charache et al[74] found that the average time until their first pain crisis on study increased from 1.5 months in patients treated with placebo to 3 months in patients treated with HU. Furthermore, the time until their second pain crisis also nearly doubled (8.8 months vs. 4.6 months).[74] The study was terminated early after 24 months because of HU's proven efficacy.[74] After this clinical trial, HU was recommended for individuals with HbSS disease and 3 or more acute pain episodes within a 1-year time frame. Despite this strong evidence for benefit, hydroxyurea remains underutilized by this patient population.[84]

Many studies have tried to estimate the specific utilization rates of HU in different age groups within the SCD population. Stettler et al[84] looked at HU utilization in adults (over 18) by examining de-identified commercial health and pharmacy claims from the Optum Normative Health Informatics database in order to identify individuals over 18 years of age who had one or more outpatient or inpatient claims and a probable diagnosis of HbSS disease based on the ICD codes that identified the encounter. More specifically, patients were selected for inclusion if they had three or more emergency department visits, hospitalizations, or both over the past year that included one of the five most common ICD codes for patients with HbSS disease who were

experiencing an acute vaso-occlusive episode, such as ICD code 517.3, which indicates HbSS disease with acute chest syndrome.[84] Hydroxyurea use was defined as the filling of one or more prescriptions for hydroxyurea after the third encounter in the ED or hospital.[84] 2,086 individuals (18 years or older) were identified with probable HbSS disease.[84] 32.5% of this identified patient population had at least three hospitalizations or ED visits in the past year, and within this population, only 15.1% had been treated with HU within three months of their third encounter.[84] At 12 months, this coverage increased to 22.9% (p = 0.002).[84] These results suggest that HU is severely underutilized by a patient population that could greatly benefit from its use, with only one quarter of patients who could benefit from HU being provided this therapy. This study did not include all patients who could benefit from HU therapy, only those with HbSS disease; this study also did not include uninsured or publicly insured individuals.[84] Individuals who resolved their pain crises without admission to the hospital or presentation to the ED were also not included. [84] All of these factors affect the generalizability of the data from this study.

HU utilization has also been examined in the pediatric SCD population. Of note, HU has only been FDA approved for children with SCD since December 2017. Creary et al[130] performed a retrospective analysis of the inpatient data within the Pediatric Health Information System (PHIS) in order to determine the utilization of HU in children with clinically severe SCD. The PHIS contains comprehensive financial and clinical data from over 48 Children's Hospital Association members, including the study site, Nationwide Children's Hospital.[130] Children who were between ages 2-18 with a diagnosis of SCD, who were discharged between January 1, 2011 and September 30, 2014 from 42 hospitals within the PHIS were included in the data analyses. The patients' most recent hospitalizations that took place within the study period were used to calculate the current rate of HU utilization. Creary et al[130] also excluded children who had an ICD-

9 code for a stroke during this period of time, because children with SCD who have acute strokes typically require longer hospitalizations and intensive care unit (ICU) stays. Additionally, HU is not prescribed to reduce strokes in SCD. For eligible participants, HU use was determined by examining the hospital data, specifically if the Pharmacy Current Procedural Terminology code for HU had been used during their hospital stay. Patients who had a history of three hospital admissions in the year prior to their most recent hospital admission or those with a history of a recent ICU admission were categorized as having severe SCD for the purposes of the data analysis.[130]   2,665 eligible participants were identified after applying these parameters and approximately 77% (2,166/2,665) had been prescribed HU during their hospital stay. 23% (499/2665) of participants had not been prescribed HU during their hospital stay. When examined by genotype, 83.5% (2,225/2,665) of patients had an ICD 9 code that diagnosed them with HbSS disease, 7.1% (190/2,665) had an ICD 9 code for HbS-beta thalassemia, 4.4 (116/2,665) had HbSC disease, and 5.0% (134/2,665) had an unspecified diagnosis of SCD. A limitation of the study is the manner in which SCD genotypes were coded using ICD 9 codes. HbS/β^0-Thal and HbS/β^+-Thal were grouped together, despite their differences in clinical severity.[130] This study helps show the utilization rate of HU within the pediatric population of clinically severe SCD.

HU use has also been evaluated in young children with SCD. Anders et al[131] conducted a retrospective cohort study that examined HU use in young children, ages 0-4, in New York State. The study population was comprised of 273 children who had been born in New York State between 2006-2009 and had a diagnosis of HbSS disease. Participants also had to be enrolled in Medicaid for a minimum of 45 of their first 48 months of life. Their clinical diagnosis was confirmed using Medicaid records. HU usage was determined from Medicaid drug claims data and "HU initiation" (the first HU prescription fill) was also measured. Anders et al[131] found that 39.5%

(108/273) of participants had been initiated on HU by the end of 2014. No statistically significant differences were found between birth year, race, or sex.

Reasons for the Underutilization of HU

As previously discussed, HU is being underutilized by individuals with SCD, with adults being less likely to take HU than children.[84,130,131] Several factors have been identified as impacting HU's underutilization, including a lack of physician training, fear of negative health events from the patient, and a lack of shared decision making with the patient.[1] The underutilization of HU has been studied in order to help identify barriers facing its implementation in the pediatric and adult SCD populations.

Brandow et al[132] surveyed pediatric hematology/oncology providers in order to learn more about HU utilization in children with SCD, as well as to identify barriers regarding HU use. A total of 220 SCD pediatric care providers completed the survey. These providers were identified through the 2008 American Society of Pediatric Hematology/Oncology (ASPHO) directory. Regarding the utilization of HU in the patient population of those surveyed, 54% reported prescribing HU to only 10-30% of their patients, 22% reported prescribing HU to 31-50% of their patients, and 9% of providers reported prescribing HU to 50-90% of their patients.

A quarter (26%) of surveyed providers reported that more than 20% of their patients/families declined HU after it was offered to them.[132] The most common reasons for this refusal were: 1) fear of negative side effects (62%), 2) fear of developing cancer (51%), 3) not wanting to take a medication (49%), 4) not wanting to be monitored for its use (laboratory monitoring) (28%), and 5) a belief that HU would not work (17%).

Regarding provider-related barriers, one theme that emerged was barriers related to patient compliance.[132] Of the providers surveyed, 86% of providers identified patient compliance regarding taking the medication as a concern and 85% of providers identified patient compliance regarding laboratory monitoring (blood tests) as a barrier. Other identified provider barriers included: a patient's expectation of negative side effects (75%), a patient being too young (68%), the provider being uncomfortable with HU as a potential carcinogen (27%), and not having enough time to explain HU's risks and benefits (16%). Eleven percent of providers surveyed also cited doubt in HU's effectiveness as a barrier to prescribing it to their patients.

Zumberg et al[133] identified similar barriers in the utilization of HU in the adult SCD population. A total of 335 self-administered surveys were completed by full-time care providers to adults with SCD in Florida and North Carolina. Of these 335 respondents, 58% (184) practiced in the community, 30% (125) practiced in a university hospital, and 12% practiced in hospitals that were affiliated with university hospitals. Regarding the utilization of HU in their patient populations, 45% of providers reported prescribing HU to less than 10% of their patients with SCD, 19% prescribed HU to 10-30% of their patients, 20% prescribed HU to 31-60% of their patients, and 11% prescribed HU to 61-90% of their patients.[133]

The surveyed providers were asked to rate how important various factors were regarding their decision to prescribe HU to a SCD patient who had a clinical indication for its use. Patient-related criteria were important in this decision. Ninety percent of providers rated patient compliance as "important" or "very important" when prescribing HU. Seventy-two percent of providers said that a patient's anticipation of negative side effects was "important" or "very important" when deciding whether or not to prescribe HU. A patient's age was rated as "important"

or "very important" by half (50%) of providers and a concern about HU as a carcinogen was rated as "important" or "very important" by 40% of providers.

Brando and Panepinto[134] suggested that "systems-level" barriers also contribute to the low utilization of HU. These barriers include lack of health care insurance, limited access to transportation and SCD care facilities, and a poor transition from pediatric to adult care.[134] These studies help provide some explanation regarding the underutilization of HU, but there is still more research that must to be done to understand further why so few individuals are taking it after its efficacy has been proven in the SCD population.

HU's Effect on ED Visits and Hospital Stays

Quarmyne et al[135] conducted a retrospective cohort study that evaluated HU's effectiveness in the pediatric population. Pediatric patients who had a diagnosis of HbSS disease or HbS/β^0-Thal who received care at the Children's Health of Atlanta SCD Program and had started taking HU in 2009 and continued until 2011 were eligible for participation. A total of 105 participants were eligible for the study. The median age of the study population was 7.5 years old. Participants had a total of 636 ED visits before starting HU, compared to 376 visits after taking HU, which meant there was a 59% reduction in ED visits. Hospitalizations in this population also decreased by 56%, from 312 pre-HU to 175 post-HU. This study effectively showed a significant decline in the utilization of acute health care after HU therapy was implemented.[135]

Lanzkron et al[136] evaluated hospital utilization in Maryland after the approval of HU using discharge data from the Maryland Health Services Cost Review Commission (MHSCRC) for the fiscal years (FY) 1995-2003. The MHSCRC database collects statistics regarding a hospital's number of discharges per year. The database included all hospitals in the state of Maryland, except

for Veterans' hospitals. Lanzkron et al[136] used ICD 9 codes to identify inpatients with SCD. They also looked at average length of stay (LOS) over this time period. The average LOS decreased from 6.16 days in FY 1995 to 4.99 days in FY 2003 (P < 0.001). This could be considered a beneficial effect of HU.

A statistically significant increase in the number of discharges for adults with SCD was observed from FY 1995 to FY 2003 (P < 0.001). It was expected that total hospitalizations would decrease after the FDA approval of HU, as the clinical trial that led to its approval observed a decrease in hospitalizations in their study population.[74,136] The observed increase in the total number of hospitalizations could be explained by the longer lifespan of individuals with SCD.[136] As these individuals live longer, they are admitted for other complications of SCD, which increases the overall hospital utilization in the SCD population.[136] It is also important to note that most adults who are eligible for HU use are not taking it.[84]

Transition of Medical Care and SCD

The median survival for HbSS is currently around 42-48 years, compared to approximately 20 years in the 1970s.[4] The introduction of newborn screening for the early detection and treatment of SCD partially explains the drastic increase in survival into adulthood.[5] Other factors affecting this increase in lifespan include improved drug therapy, preventative measures, and more timely medical interventions.[5] Because of this increased survival, there is now a need for adult care providers to care for adolescents and young adults (AYA) as they move from the pediatric care facility to adult care.

Typically, these individuals must transfer their care from a pediatric care facility to an adult care facility between ages of 18-22 years. The process of a medical transition can be defined as

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"the process of changing from a pediatric to an adult model of health care."[6] These transitions are often determined by an individual's biological age, rather than their independence or readiness to transition.[7] Quinn et al[5,70] found that AYA who had recently transitioned their care were at a higher risk for death. This could be explained by an accumulation of organ damage over time or an unsuccessful transition to adult care.[64] Inconsistent care or loss of sickle cell expertise in adult care facilities could also be an explanation for this higher mortality rate.[71]

ED Utilization in the Pediatric and Young Adult Population

The AYA age group has also been shown to utilize symptomatic care, such as visiting emergency departments (EDs), more frequently than other age groups.[72] Brousseau et al[72] used state inpatient and ED databases in eight states in the US to conduct a retrospective cohort study. All of the ED visits and hospital stays used in data analysis were related to SCD complication. The study included a total of 21,112 patients, of which 7,250 were between the ages of 18 and 30 years old. This age group was found to have the highest ED utilization rates, averaging 3.61 visits per year.[72] Nearly a quarter (22%) of individuals in this age group had 3-10 acute care encounters per year, compared to only 12.6% of their 10-17 year old peers. 7.4% of individuals in the 18 - 30-year-old age group had 10 or more acute care encounters per year, compared to only 1.1% of those in the 10-17-year-old age group. This study helps show the increase in morbidity during the AYA period and this age group's increased ED utilization.

Singh et al[125] conducted a retrospective longitudinal study that estimated the ED visit rate of 609 patients with SCD over a five year period. Data from the Wisconsin state Medicaid data was used for the years 2011-2015. Patients in the study had to have at least one sickle cell pain-related ED visit and had to be continuously enrolled in Wisconsin state Medicaid during the

timeframe of the study. The study population ranged from ages 0-45 years old. The group was further divided into four age groups: children, ages 0-18 (n=248), a transition group, which included patients who had turned 19 years old during the study (n=54), young adults, ages 19-30 (n=170), and adults, ages 31-45 (n=137). There was overlap between the transition group and the 19-30-year-old group. Singh et al[125] found that the transition-age group and the young adult group relied on ED visits more than children (p=0.0014). Children had an average ED Visit of 1.74 visits per year, while the transition group had an average of 8.24 ED visits per year, and the young adult group had an average ED visit total of 9.81 visits per year. Although this study shows an increase in utilization in the transition and young adult group, the researchers did not separate AYAs (18-24 years old) from the young adult population, which limits its generalizability to the AYA population.

Aims of the Current Study

In the city of Pittsburgh, there is both a pediatric (Children's Hospital of Pittsburgh of UPMC) and an adult care facility (Adult Sickle Cell Clinic of UPMC) that provides multidisciplinary care for individuals with SCD. In Pittsburgh, AYA typically make the transition to the Adult Sickle Cell Clinic by age 21. One aim of this study is to assess the frequency of ED visits in the AYA population (ages 15-20 years old) in comparison to children ages 6-11 years old. This will allow both clinics to see if there is a higher utilization of ED visits in the AYA population and identify reasons behind its utilization. The results of this study could also have implications for the transition program in Pittsburgh and allow modifications to be made based on the findings. The current study also aims to examine the utilization rate of HU in pediatric patients with HbSS disease and HbS/β^0-Thal. Identifying the clinic-specific utilization rate in the Pediatric Sickle Cell

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Clinic could help its health care professionals by assessing if their clinic population has a utilization rate that is similar to previously published rates of HU use in the pediatric population and help determine possible HU education or other interventions should the utilization rate be lower than expected.

5.2   METHODS

5.2.1 Description of the Data Set

The Sickle Cell Database is an online database that is maintained by the Pediatric Hematology Department of the Children's Hospital of Pittsburgh of UPMC (CHP). The clinical sickle cell database was created in 1999. Patient demographics including name, database ID number, medical record number, and sickle cell disease type are uploaded from the electronic medical record (EMR). Other information must be manually entered by the clinical team, which includes clinic appointments, ED visits, hospitalizations, medications prescribed specifically including HU and penicillin, and outside referrals. This database includes data from individuals who are currently or have previously been seen in the Pediatric Sickle Cell Clinic at CHP. All of the individuals in the database have a diagnosis of sickle cell disease (SCD) and are followed by the clinic for management of this disease. There are currently 566 patients entered into the database, although not all of these individuals have "active" status, which means they have either transitioned to adult care or relocated. The database is used by health care professionals within the Pediatric Sickle Cell Department to help track various trends such as outpatient clinic visits, ED

visits, inpatient visits (hospitalizations) within a certain period of time. It is automatically synced with the EMR and additional data is manually entered by clinical staff at the end of each quarter.

For the purposes of the current study, a subset of data was collected from the clinical sickle cell database. This data included database ID number, patient age at ED visit, patient current age, sickle cell disease type, ED visit date, and prescription of HU. The study was reviewed and approved by the University of Pittsburgh Institutional Review Board under a modified IRB on April 26, 2018, IRB# PRO17020086 (See Appendix D).

5.2.2. Selection Criteria

The data set for the analysis included 276 patients from the Sickle Cell Database. In 2012, the website itself was updated and manual entry of the aforementioned data by staff members became more consistent, so 2012 was chosen as the start of the data analysis. The data analysis included patients who had "active status," meaning that they had been seen in the Pediatric Sickle Cell Clinic any time between January 1st, 2012 to December 31st, 2017.

This analysis excluded data for the time period after individuals moved away, after transitioned to adult care facilities, or after the date of death. The two groups used for comparison for aim one were children ages 6-11 years old, and AYA who were 15-20 years old. These two age groups were selected in order to compare two groups of patients over a similar six-year age range, thus with similar sample sizes. Because patients are typically transitioned before they turn 21 years old at the Pediatric Sickle Cell Clinic, the data collection for AYA was limited to ages 15-20 for the purposes of this study. Patients who were five years old or younger at the time of ED visit were excluded from the data analysis, because these younger children with SCD often present to the ED for very different medical concerns compared to patients older than 6 years old. For

example, splenic sequestration and fever concerning for pneumococcal sepsis are common reasons for ED visits in young children with SCD that are more rare after age 6 years of age.[1] The 12-14 year old patients in the data set were excluded from the analysis in order to better match the younger age range, and thus sample size, with the time period for the AYAs that was limited to 6 years due to the transition age (age range: 15 through 20 year old). The exclusion of these patients would also emphasize the difference between the younger SCD and AYA age groups as well as reduce the number of patients who were present in both age groups.

Several patients are followed by the Sickle Cell Clinic for diagnoses other than SCD. For example, individuals with a genotype of HbS-Hereditary Persistence of Fetal Hemoglobin (HPFH) were excluded from the analysis, because this genotype does not have the same clinical symptoms as SCD.

5.2.3 Preparation of Data

The original data was exported from the clinical sickle cell database into a Microsoft Excel spreadsheet. The database collects a large set of personal and clinical information such as patient name and date of birth. This clinical data automatically populated into the original data file, but only a subset of the data was saved for research purposes. Research data was stored on a secured drive on the CHP server. The research data file saved for this study included database ID number, patient age at ED visit, patient current age, sickle cell disease type, ED visit date, and prescription of HU.

For aim one, the variable "Patient Age at ED Visit" was used to determine which patients were included in the analysis. If a patient was between the ages of 6 and 11 for the "Patient Age at ED Visit" category, they were included in the 6-11-year-old age group. Individuals who had an

age ranging from 15-20 in the "Patient Age at ED Visit" category were included in the AYA group (15-20-years old). Any individuals outside of these parameters (e.g. patients under five years old and patients who were 12-14 years old for "Patient Age at ED Visit") were excluded from the data analysis. Once these criteria were applied to the data set, there were 83 patients in the 6-11-year-old age group and 99 individuals in the 15-20-year-old age group. Of note, three patients were present in both age groups.

ED Visit Rate

A yearly ED Visit Rate was calculated for this analysis for each individual in the 6-11-year-old group and the 15-20-year-old group (AYA group). This was accomplished by dividing an individual's total number of ED visits by the number of years that they were active in the database within this age group. For example, patients who moved or transitioned to the adult program and were not in the program for the total six years were divided by the smaller number of active years.

Coded Variables

Patient Age at ED Visit, Severity of Disease, and Prescription of Hydroxyurea were all coded as categorical (yes/no) variables for the purposes of this analysis.

1. Patient Age at ED Visit

Two age groups were created 1) 6-11 years old 2) 15-20 years old. Individuals in the first age group were all assigned 0's and everyone belonging to the AYA ages group (15-20 years old) was assigned a 1. The 6-11 year olds were selected for the study because they were 1) in the

database for the six-year time period and 2) they had surpassed the age at which they are at the highest risk for ED visits due to complications that primarily affect only very young children.[1] The 15-20 year old group was chosen because these ages are within the AYA period, which is the age range that was being compared to the pediatric patient group.

2. Severity of Disease

Each individual was identified by their specific diagnosis of SCD. This was further categorized into a "disease severity." HbSS disease or HbS/β^0-Thal are clinically similar and have the most severe symptoms and were therefore grouped together.[1] Therefore, individuals were placed into one of two groups based on the clinical severity of their specific SCD diagnosis: severe disease or less severe disease. The National Heart, Lung, and Blood Institute's (NHLBI) Management Guidelines were used to help determine these clinical severity groupings.[1] HbSS disease or HbS/β^0-Thal were grouped together and coded as "1's" for severe disease, and other genotypes, including HbSC disease and HbS/β^+-Thal were coded as "0's" for less severe disease.

3. Hydroxyurea Use

From the original data set of 276, 163 participants had a genotype of HbSS disease or HbS/β^0-Thal. These genotypes were selected because HU is recommended for individuals with severe SCD.[1] A new data sheet was created for these 163 participants. These 163 individuals were coded for prescription of hydroxyurea. If the individual in this group had been prescribed HU at any time within this six-year timeframe, this was coded as a 1 for "yes, has been prescribed hydroxyurea." If an individual in either severe disease group had not been prescribed hydroxyurea

within the full 6-year timeframe, this data was coded as a 0 for "No, has not been prescribed hydroxyurea within this timeframe."

Data Analysis

Data analysis was performed using JMP Pro 13 for Mac. A chi-squared test was performed to compare age (ages 6-11 vs. ages 15-20) to ED visit rate. Descriptive statistics were used to calculate the utilization of HU in individuals with severe SCD.

5.3   RESULTS

Aim 1 Results

A total of 83 patients were in the 6-11-year-old age group that had at least one ED visit during this timeframe (Table 3). Of these 83, 57.8% (48/83) had a diagnosis of HbSS disease, 25.3% (21/83) had HbSC disease, 8.4% (7/83) had HbS/β^0-Thal, and 8.4% (7/83) had HbS/β^+-Thal. Approximately 66% (55/83) of these individuals had a diagnosis of severe SCD (HbSS disease or HbS/β^0-Thal). In this age group, the mean age at ED visit was 8.0 years old (SD = 1.7) and the mean ED visit rate was 0.8 visits/year for the subset of patients who visited the ED (n=83; See Figure 1). The lowest ED visit rate was 0.2 visits per year and the highest ED visit rate was 4.0 visits/year. There were also an additional 26 individuals in this age group who never had an ED visit between ages 6 and 11 years old (24% or 26/109). Of those who did not have an ED visit, 30.8% (8/26) had a diagnosis of HbSS disease, 53.8% (14/26) had a diagnosis of HbSC disease, 7.7% (2/26) had HbSβ^0 Thalassemia, and 7.7% (2/26) had HbSβ^+Thalassemia (Table 3).

Approximately 39% (10/26) of individuals who did not present to the ED had a diagnosis of severe

SCD (HbSS disease or HbSβ^0 Thalassemia) compared to 66% (55/83) with severe disease who

did present to the ED between the ages of 6 and 11 years (Table 3).

Table 3: Summary of Two Age Groups (6-11 and 15-20 year old) Characteristics

	6-11 year olds with ED Visits (N=83)	6-11 year olds with No ED Visits (N=26)	15-20 year olds with ED Visits (N=98)	15-20 year olds with No ED Visits (N=15)
	Total in Age Group = 109		**Total in Age Group = 113**	
Sickle Cell Diagnosis **HBSS** **HBSC** **HbSβ^{0}Thal** **HbSβ$^+$Thal** **HbS-O-Arab**	48 (57.8%) 21 (25.3%) 7 (8.4%) 7 (8.4%) 0 (0%)	8 (30.8%) 14 (53.8%) 2 (7.7%) 2 (7.7%) 0 (0%)	51 (52.0%) 37 (37.8%) 0 (0%) 9 (9.2%) 1 (1.0%)	5 (33.3%) 8 (53.3%) 0 (0%) 2 (13.3%) 0 (0%)
Severe Disease (HbSS or Hbβ^{0}Thal)	55 (66.3%)	10 (38.5%)	51 (52.0%)	5 (33.3%)
Median ED Visit Rate	0.5 visits/year	-	1.2 visits/year	-
Mean age at ED Visit (SD)	8.0 (1.7)	-	17.2 (1.8)	-
Mean ED Visit Rate	0.8 visits/year	-	1.9 visits/year*	-
ED Visit Rate Range	0.3-4.0 visits/year	-	0.2-11.0* visits/year	-

*Note: Outlier of 40.5 visits/year for a single individual was excluded from the data analysis.

There were 98 patients in the 15-20-year-old age group who experienced at least one ED

visit (Table 3). Of these 98, 52.0% (51/98) had a diagnosis of HbSS disease, 37.8% (37/98) had

HbSC disease, 9.2% (9/98) had HbSβ$^+$Thalassemia, and 1 patient had HbS-O-Arab disease. The

mean age at ED visit was 17.2 (SD = 1.8) and the mean ED visit rate was 1.9 visits/year (Figure 1). The lowest ED visit rate was 0.2 visits per year. While the highest ED visit rate was 40.5 visits/year, this was excluded as an outlier for data analysis and the highest remaining ED visit rate was 11.0 visits/year in the remaining group. In addition, there were 15 AYA with SCD who did not visit the ED between the ages of 15 and 20 years. Thus, approximately 13% (15/113) of patients ages 15-20 years old did not have an ED visit during this timeframe while 87% of patient in this AYA age group did present to the ED. Of those who did not have an ED visit, 33.3% (5/15) had a diagnosis of HbSS disease, 53.3% (8/15) had a diagnosis of HbSC disease, and 13.3% (2/15) had HbSβ$^+$Thalassemia. Approximately one-third (5/15) of these individuals not presenting to the ED had a diagnosis of severe SCD (HbSS disease or HbSβ^0 Thalassemia) compared to over half (52/98) of the older group having severe SCD with a history of ED visits.
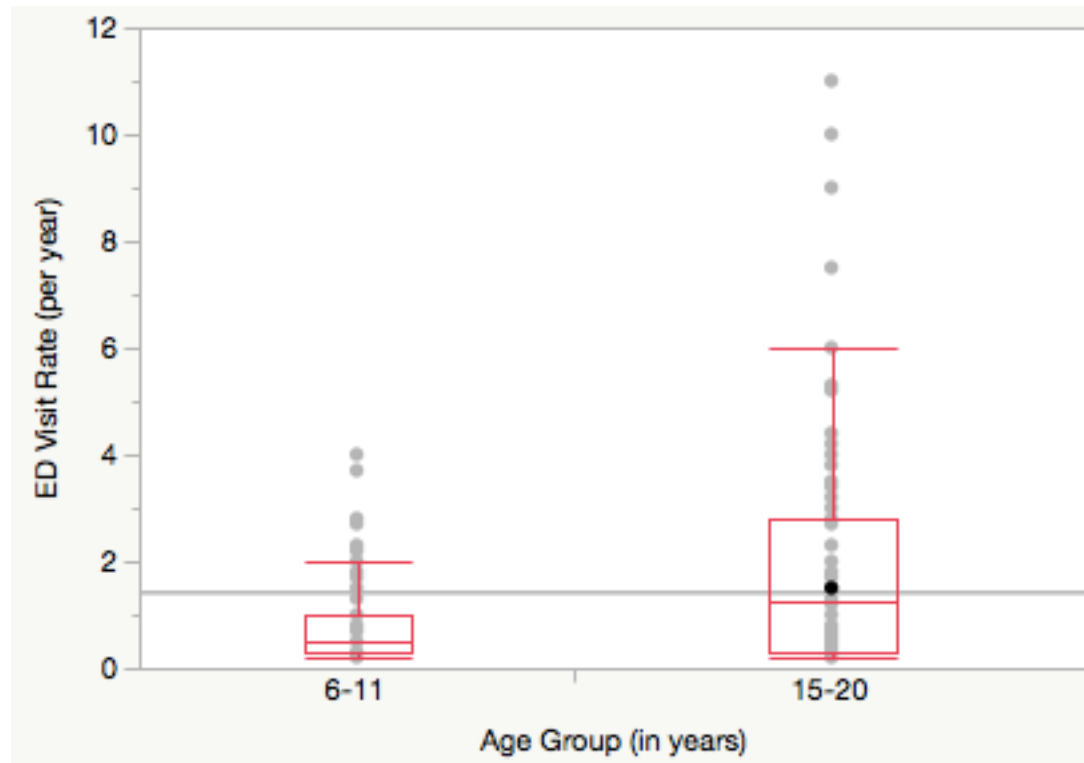

Figure 1: Box and Whisker Plot of ED Visit Rate for 6-11-year olds and 15-20-year olds

There was a significant relationship between frequency of ED visits and age as assessed by Chi-squared analysis (P = 0.004) (Table 5). Patients in the 6-11-year-old age group had a median ED visit rate of 0.5 ED visits/year, in comparison to the AYA group (15-20-years old) whose median ED visit rate was 1.2 ED visits/year.

Table 4: Results for the Relationship between Age and ED Visit Rate

N	DF	Chi-Square Value	P value
182	34	59.97	0.004

Three of the patients in the ED visit data set were included in both the 6-11-year-old age group and the 15-20-year-old age group. In the 6-11-year-old data set, their ED visit rates were 0.7, 0.3, and 0.5. In the 15-20-year-old data set, all three of the patients' ED visit rates were only 0.2/year. There were also another 7 patients that did not visit the ED during this timeframe and who were included in both the 6-11-year-old group and the AYA group with ED visit rate of 0 in both older and younger timeframes.

Aim 2 Results

The second aim of the study examined the utilization rate of HU in pediatric patients with HbSS disease and HbS/β^0-Thal in the pediatric sickle cell database. Of the 276 individuals in the original data set, 163 (59.1%) were determined to have severe disease, defined as HbSS disease or HbS/β^0-Thal. 93.9% (153/163) of patients had a diagnosis of HbSS disease, while 6.1% (10/163) had a diagnosis of HbS/β^0-Thal (Table 6). 65.0% (106/163) of patients with severe SCD in the

Sickle Cell Database were prescribed HU in the past six years. When looking at each genotype, 70.0% (7/10) of patients with HbS/β^0-Thal and 64.7% (99/153) of patients with HbSS disease had been prescribed HU within the pediatric program. When looking specifically at the two ages groups, 89.2% (58/65) of individuals ages 6-11 years old with severe SCD were prescribed HU, while 67.3% (35/52) of individuals ages 15-20 years old with severe SCD were prescribed HU (Table 5).

Table 5: Prescription of HU in Individuals with Severe SCD

Genotype	N (%)	Prescribed HU All Ages	Prescribed HU 6-11 years old	Prescribed HU 15-20 years old
HbSS	153 (93.9)	99 (64.7)	50/56 (89.3)	35/52 (67.3)
HbS/β^0-Thal	10 (6.1)	7 (70.0)	8/9 (88.9)	-
Total	163	106 (65.0)	58/65 (89.2)	35/52 (67.3)

5.4 DISCUSSION

The current study found that there is a relationship between ED visit rate and a patient's age, and that AYA have higher median and average ED visit rate than the pediatric SCD population. The average ED visit rate for the 15-20-year-old group was 1.9 visits per year, compared to an average of 0.8 visits/year in the 6-11-year-old group. These findings are consistent with the literature, which reports that the AYA age group utilizes symptomatic care more frequently than other age groups.[72] Singh et al[125] found higher rates of ED utilization in patients

who had transitioned to adult care during the study in their longitudinal study of ED visit rates. The two groups that were found to have the highest ED utilization rates were the transition group (who were 19 years old at transition) and the young adult group (ages 19-30).

Singh et al[125] also found that the transition-age group and the young adult group relied on ED visits more than children (p=0.0014). While the age ranges do not quite align between this study and the current study, both studies' results show a significant difference in ED utilization between AYA and children. Singh et al[125] found that children (ages 0-18) had an average ED visit of 1.74 per year, compared to the transition group and young adult groups (8.24 and 9.81 visits per year, respectively). These averages are much higher than the current study's average ED visit rates of 0.8 per year (6-11 years old) and 1.9 per year (15-20 years old). A potential explanation for this difference is the difference in the division of age groups between the two studies. The pediatric age group that Singh et al[125] used in their study was for ages 0-18, which, within the context of the current study, contains some of the AYA population (15-18 within this group). Additionally, their "young adult" population included individuals with SCD up to age 30 years old, which is an older age range than the current study and it is possible that ED utilization continues to increase with age. This limits the ability to draw direct comparisons between the studies, although the direction of the trend was the same (more ED visits as participants age).

The findings in the current study indicate that there was a difference in ED utilization between the two age groups. The ED utilization rate in the 15-20-year-old age group was double that of the 6-11-year-old age group (1.8 vs. 0.9 visits per year). A possible explanation for this is that ED utilization increases in the SCD population before the age of 18. In many previous studies, the "child" group has included pediatric patients with SCD from ages 0-18 and has not made any distinctions between these age groups. Brousseau et al[72] did distinguish between the child and

adult age group in their study when evaluating ED visits and hospitalizations for SCD. By using

ICD-9 and Clinical Software Classification codes, they conducted a retrospective cohort study of

21,112 patients and found that the average ED visit rate gradually increased over time until age

30, after which the average ED visit rate decreased. Individuals ages 1-9 years old averaged 1.50

ED visits per year, patients 10-17 years old averaged 2.04 ED visits per year, and individuals age

18-30 years old averaged 3.61 ED visits per year.[72] The total ED visit rate decreases with

increasing age in patients older than 30 years old, which is beyond the upper limit of the AYA age

range of 27 years old. This study shows that while there is increased ED utilization for AYA, this

trend does not continue despite overall increasing ages.

The second goal of the study was to assess HU utilization in the pediatric SCD population.

HU was prescribed to approximately 65% of individuals with severe SCD. Previous studies have

reported rates of approximately 40%.[130] In the study that reported the rate of 39.5%, the study

population was a group of infants and toddlers (ages 0-4).[131] In the second study by Creary et al[130],

the study population ranged from ages 2-18, but only assessed patients who had been admitted

rather than all patients followed by the program. This age range is more consistent with the current

study, which includes patients from ages 0-21 in its analysis. If using the rate determined by Creary

et al (77%), HU utilization in the current study population is below this rate. It is important to note

the differences in data collection. For this study, HU prescriptions were measured over a six-year

period of time in individuals who were active patients in a sickle cell outpatient clinic, whereas

the study by Creary et al utilized ICD-9 codes obtained from individuals during a hospitalization

related to their SCD diagnosis. Because Creary et al[130] used data from a hospitalized population

of individuals with SCD, it is likely that these patients' utilization rates were higher than a non-

hospitalized population. In both studies, it is impossible to measure medical compliance from this data.

Public Health Significance

Although the National Heart, Lung, and Blood Institute (NHLBI)'s expert panel on SCD currently recommends that all pediatric patients over the age of 9 months old with severe SCD (HbSS or HbS-Beta-0-Thal) take HU[1], the utilization rate of HU in the overall population of individuals with SCD falls well below its optimal rate. Several studies have looked at the reasons behind this underutilization. Providers have cited patient refusal of HU due to a fear of negative side effects, including the development of cancer, not wanting to undergo laboratory monitoring for starting a new medication, and a belief that HU will not work.[132] Providers also cited their own reasons for not prescribing HU to eligible patients. These include their patient's anticipation of negative side effects, a patient's age (being too young), provider discomfort with prescribing HU (thinking it is a potential carcinogen), and doubt in HU's effectiveness.[132] There are also "systems-level" barriers that could contribute to HU's low utilization rate.[134] These barriers include limited access to transportation and SCD care facilities, a poor transition from pediatric to adult care, and a lack of health insurance.[134]

From a public health perspective, it is important to increase HU in the eligible population to help improve their quality of life and potentially decrease the amount of pain crises and ED visits they have. Potential champions for the use of HU in SCD include community based organizations such as CSCF, NBS programs and/or SCD care facilities. These programs and facilities could provide parents/guardians with information regarding HU and its efficacy. This

would also allow eligible infants with SCD to start HU at an early age, which could decrease the amount of SCD-related complications they see throughout life.

The use of HU has also been shown to decrease the number of ED visits for pain.[135] This has important implications for health care costs. Individuals with SCD have been shown to have the highest average health care cost of all chronic diseases.[136] Lanzkron et al[136] estimated that the total charges for all SCD-related ED visits for 2006 were $356 million. Including hospital admissions, this number climbs to $2.4 billion.[136] By increasing the implementation of HU in eligible SCD individuals, this financial burden on the health care system and families could be reduced.

Potential interventions to increase the use of HU include provider, patient, school and community education on both SCD and the proven efficacy of HU. Given the lack of comprehensive adult sickle cell programs, primary care providers often assume the role of general sickle cell care after transition from a pediatric program and would be an ideal target for education on the use of HU in individuals with sickle cell disease. Once these providers are properly educated on HU, they can educate their patients about the drug and provide them with accurate information. An increased understanding regarding the efficacy and safety of HU should help increase its use and dispel misconceptions about the drug, such as the lack of data to support concerns for increased carcinogenesis in individuals with SCD after long-term use.[137]

Lastly, ED utilization tends to increase in the AYA population.[125] These individuals may be undergoing their transition to adult care and participating in a transition program. These individuals could benefit from a discussion of HU during their transition program. This would allow the AYA to fully understand the reasons for its use, importance of compliance, and how HU could benefit them in the future.

Study Limitations

For the first aim of the study, when calculating ED visit rate, it was assumed that all individuals, except those who had transitioned, had been at the clinic for the entire six-year period of time. Realistically, this may not be the case for every patient. The researcher was unable to track precisely when a patient's first or last clinic visit was within the database itself, which limits the validity of this set of data.

One of the main limitations of the second aim of the study is the database's available information on HU prescriptions. If someone has been prescribed a medicine, this does not mean that the individual will take the medicine or adhere to a regular pattern of use. Assessment of medical adherence is challenging and this data was not tracked for the patients within this database, which limits the validity of the data. HU prescriptions were also coded a categorical "Yes/No" variable for a six-year period of time, which limits the data even further. By doing so, a large assumption was made, namely that an individual who was prescribed HU was 1) regularly taking HU and 2) taking HU for the entirety of this period of time. Another limitation of the study was that the data on HU prescriptions and ED visits were not connected to each other within the study population due to constraints of the data input. Because of this, the researcher could not compare ED visit rates to HU at each specific visit in this study population.

This study used data that are from single tertiary care academic pediatric hospital, which is located both within a major metropolitan area, although this center serves all of Western Pennsylvania. This limits the data's generalizability to more primary care and nonacademic settings. In areas where there are not designated sickle cell care centers, the data collected could look quite different. For instance, there may be a higher ED visit rate in these areas because individuals with SCD must rely on their PCP or another provider without SCD expertise for their

care. This could also impact the likelihood of these care providers prescribing HU and other preventive care to their patients. The misconception of providers regarding HU and its side effects, namely that it could cause cancer, has been identified as a barrier to the underutilization of HU.[132,134] Such misconceptions could have real consequences for individuals with SCD who would benefit from HU in areas without SCD expertise. These provider beliefs could also influence how their patients feel about HU, which could make patients less open to being prescribed the medication.[134]

There is also room for human error in this study. Because some of the data used in the analysis was entered manually by the clinical team, data entry errors are possible. The data was also refined for analysis and coded, so errors with the coding of the data are possible as well.

Future Research

Future directions could include evaluating the patient perspectives regarding HU use in order to identify barriers and develop potential solutions. Then the use of HU pre- and post-intervention could be compared. Medical adherence to HU use could also be assessed in a future study. This would allow the Pediatric Sickle Cell Team to see if the medical adherence for HU is as high as its prescription rate within the population and identify barriers to compliance. The relationship between age and HU use could also be further explored, to see if it is utilized more within a certain age group and whether HU use is linked to specific ED visits, hospitalizations or the development of specific sickle cell-related complications. Another question of interest is whether individuals with severe SCD (HbSS or H-S-Beta-0-Thal) who are taking HU are less likely to visit the ED compared to individuals with severe SCD who are not taking HU. This would

allow comparisons to be made to the literature to see if HU use decreases the amount of ED visits in this specific pediatric sickle cell population, as has been previously observed.[135]

Conclusion

This study found a significant relationship between age and ED visit rate (P = 0.0039). AYA (15-20 years old) visited the ED twice as frequently as children ages 6-11 years old. This is consistent with literature reporting an increased ED utilization rate in the AYA SCD population.[124] Approximately 24% (26/109) of patients ages 6-11 did not have an ED visit during this timeframe, in comparison to only 13% (15/114) of patients ages 15-20 years old.

Regarding hydroxyurea use in the study population, 65% (106/163) of individuals who were eligible for HU use had been prescribed HU during the timeframe of the study. Although this rate is high, hydroxyurea still remains underutilized by the SCD population as a whole.[134] By addressing patient and provider barriers, HU's implementation is likely to further increase, which could potentially decrease hospitalizations and ED visits 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: 3/19/2018

IRB#: PRO17110603

Subject: Transition in Sickle Cell Disease

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.(5)
45 CFR 46.110.(7)

The IRB has approved the waiver for the requirement to obtain a <u>written</u> informed consent for participation of health care providers and staff.

The risk level designation is Minimal Risk.

Approval Date: 3/19/2018
Expiration Date: 3/18/2019

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.

APPENDIX B: SCRIPT FOR INTERVIEW CONSENT

Script for Interviews

My name is Emily Mazzei. I am a Masters student in the genetic counseling program at the University of Pittsburgh. For my Master's thesis, I am conducting research on the transition to pediatric to adult care in adolescents and young adults with sickle cell disease. I am interested in your experiences as a care provider. The purpose of this research is to learn more about the transition process and the challenges that these adolescents and young adults, as well as you, a care provider, face during this process.

Your participation will involve one informal interview that will last between thirty minutes to an hour. Questions asked will pertain to your opinions and experiences regarding the topic of transition. There is no direct benefit to you for participating in this study.

This research has a risk of breach of confidentiality. We will replace your name with a unique code when we collect any data for this study, so your name will not be included on any of our data files. We will keep a separate document that will link your name with the code always in a separate secure location. I will do everything I can to protect your privacy. Your identity and/or personal information will not be disclosed in any publication that may result from the study. Your responses will not be shared with The Children's Sickle Cell Foundation. All paper records related to your involvement in this research study will be stored in a locked file cabinet. 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.

I will give you a copy of this script, which has my contact information on it, should you have any questions or concerns. You may choose not to answer any question. Participation is voluntary, and you have the right to withdraw or to not answer questions.

Do I have your permission to begin the interview?

Contact information:
Emily Mazzei
Emm182@pitt.edu

APPENDIX C: SURVEY MEASURES AND DATA COLLECTION FORM

Last summer, you participated in The Children's Sickle Cell Foundation's transition program. This survey is to learn about your experience with this program, as well as your thoughts on the topic of transition. Your feedback will help The Children's Sickle Cell Foundation learn about the strengths and weaknesses of their program, and also help health professionals learn about your experiences with the process of transition. This survey will take 10-15 minutes of your time. Your responses are voluntary and will be kept confidential. Responses will not be identified by individual. If you have any questions or concerns, please contact Emily Mazzei, the student collecting and analyzing this data, at emm182@pitt.edu.

Thank you for your participation.

Instructions: Please answer the questions below. The first few questions are asking about your experience transitioning from a children's hospital to an adult facility.

How old should a person be when he/she transitions to the adult facility?

Your response: _____

Please explain why the age you chose would be a good time to transition.
Your response:
_____
_____
_____

What was the biggest challenge for you when you moved from the pediatric (children's) hospital to the adult facility?
Your response:
_____
_____
_____
_____

How could this have been improved?
Your response:
_____
_____
_____
_____

At this moment, what is the biggest challenge for you with the healthcare you are receiving?
Your response:

_____
_____
_____

How could this be improved?
Your response:

_____
_____
_____
_____
_____ _____ _____

What is the difference for you between going to a pediatric (children's) facility and an adult facility for your check ups and care?
Your response:

_____
_____
_____
_____
_____ _____ _____

This concludes the section about transition. In this section, the questions that are asked are about your experience with The Children's Sickle Cell Foundation's transition program.

What did you like about the transition program?
Your response:

_____
_____
_____
_____ _____ _____

What was your least favorite part about the transition program?
Your response:

_____
_____
_____
_____ _____ _____

How could the program be improved?
Your response:

_____
_____
_____
_____
_____ _____ _____

This is the end of the survey. Thank you for your participation. Please hand this paper back to the person who gave it to you.

Please fill out this form to help us see what you already know about your health, using health care and areas that you need to learn more about. If you need help completing this form, please let us know.

Date:

Name: **Date of Birth:**

Transition and Self-Care Importance and Confidence *On a scale of 0 to 10, please circle the number that best describes how you feel right now.*

How important is it to you to manage your own health care?

0 (not)	1	2	3	4	5	6	7	8	9	10 (very)

How confident do you feel about your ability to manage your own health care?

0 (not)	1	2	3	4	5	6	7	8	9	10 (very)

My Health *Please check the box that applies to you right now.*	Yes, I know this	I need to learn	Someone needs to do this... Who?
I know my medical needs.	☐	☐	☐
I can explain my medical needs to others.	☐	☐	☐
I know my symptoms including ones that I quickly need to see a doctor for.	☐	☐	☐
I know what to do in case I have a medical emergency.	☐	☐	☐
I know my own medicines, what they are for, and when I need to take them.	☐	☐	☐
I know my allergies to medicines and the medicines I should not take.	☐	☐	☐
I can explain to others how my customs and beliefs affect my health care decisions and medical treatment.	☐	☐	☐
Using Health Care			
I know or I can find my doctor's phone number.	☐	☐	☐
I make my own doctor appointments.	☐	☐	☐
Before a visit, I think about questions to ask.	☐	☐	☐
I have a way to get to my doctor's office.	☐	☐	☐
I know I need to show up 15 minutes before the visit to check in.	☐	☐	☐
I know where to go to get medical care when the doctor's office is closed.	☐	☐	☐
I have a file at home for my medical information.	☐	☐	☐
I know how to fill out medical forms.	☐	☐	☐
I know how to get referrals to other providers.	☐	☐	☐
I know where my pharmacy is and how to refill my medicines.	☐	☐	☐
I know where to get blood work or x-rays done if my doctor orders them.	☐	☐	☐
I carry important health information with me every day (e.g. insurance card, allergies, medications, emergency contact information, medical summary).	☐	☐	☐
I understand how health care privacy changes at age 18 when legally an adult.	☐	☐	☐
I have a plan so I can keep my health insurance after 18 or older.	☐	☐	☐

18

Data Collection Form
Subject Code:

Survey: "Got Transition"
Section: Transition and Self-Care Importance and Confidence
Key for Answers
0 = not very important; 10 = very important

Question #	Initial Answer (0-10)	2nd Answer (1-10)	Change? Y/N	Notes
1				
2				

Section: My Health
Key for Answers:
1= Yes, I know this
2 = I need to learn this
3 = Someone needs to do this... who?

Question #	Initial Answer (1/2/3)	Second Answer (1/2/3)	Change? Y/N	Notes
1				
2				
3				
4				
5				
6				
7				
	Total: 1s 2s 3s Blanks	Total: 1s 2s 3s Blanks		

Survey: CSCF Transition Care Plan

Question #	Answered:
1	Answered/Left blank
2	Yes/No
3	Yes/No
4	Yes/No
5	Parent or Guardian/Yourself

APPENDIX D: IRB APPROVAL LETTER FOR PUBLIC HEALTH ESSAY

University of Pittsburgh
Institutional Review Board

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

Memorandum

To: Cheryl Hillery, MD
From: IRB Office
Date: 4/26/2018
IRB#:   MOD17020086-01 / PRO17020086
Subject: EFFECT OF STANDARD OF CARE CHANGES ON THE NO-SHOW RATE IN A
          SICKLE CELL CLINIC

The University of Pittsburgh Institutional Review Board reviewed and approved the requested modifications by expedited review procedure authorized under 45 CFR 46.110 and 21 CFR 56.110.

Modification Approval Date: 4/26/2018
Expiration Date: 3/15/2020

The following documents were approved by the IRB:
Add new study personnel: Emily Mazzei, co-Investigator Atinuke Aramide Dosunmu-Ogunbi, co-Investigator Natalie Thurman, research nurse coordinator New Aim: Assess the relationship between age, sickle cell disease severity and medication compliance with appointment no-show rate and hospital/emergency department utilization.

BIBLIOGRAPHY

1. National Institute of Health. Evidence-Based Management of Sickle Cell Disease: Expert Panel Report. U.S. Department of Health and Human Services. https://www.nhlbi.nih.gov/health-topics/evidence-based-management-sickle-cell-disease. Published 2014.

2. Andemariam B, Owarish-Gross J, Grady J, Boruchov D, Thrall R, Hagstrom JN. Identification of Risk Factors for an Unsuccessful Transition from Pediatric to Adult Sickle Cell Disease Care. *Pediatr Blood Cancer*. 2014;61:697-701. doi:10.1002/pbc

3. Scott RB. Health Care Priority and Sickle Cell Anemia. *J Am Med Assoc*. 1970;214(4):731-734.

4. Platt O, Brambilla D, Rosse W, et al. Mortality in Sickle Cell Disease. *N Engl J Med*. 1994;330(23):1639-1644.

5. Quinn CT, Rogers ZR, Mccavit TL, Buchanan GR. Improved Survival of Children and Adolescents with Sickle Cell Disease. *Blood J*. 2010;115(17):3447-3452.

6. What Is Health Care Transition? The National Alliance to Advance Adolescent Health. http://gottransition.org/providers/index.cfm. Published 2018. Accessed February 12, 2018.

7. McPherson M, Thaniel L, Minniti C. Transition of Patients with Sickle Cell Disease from Pediatric to Adult Care: Assessing Patient Readiness. *Pediatr Blood Cancer*. 2009;52:838-841.

8. Speller-Brown B, Patterson Kelly K, VanGraafeiland B, et al. Measuring Transition Readiness: A Correlational Study of Perceptions of Parent and Adolescents and Young Adults with Sickle Cell Disease. *J Pediatr Nurs*. 2015;30(5):788-796. doi:10.1016/j.pedn.2015.06.008

9. Benson JM, Therrell BL. History and Current Status of Newborn Screening for Hemoglobinopathies. *Semin Perinatol*. 2010;34(2):134-144. doi:10.1053/j.semperi.2009.12.006

10. Manwani D, Frenette PS. Vaso-occlusion in Sickle Cell Disease: Pathophysiology and Novel Targeted Therapies. *Blood*. 2013;122(24):3892-3898. doi:10.1182/blood-2013-05-498311.This

11. Hassell KL. Population Estimates of Sickle Cell Disease in the U.S. *Am J Prev Med*. 2010;38(4S):S512-S521. doi:10.1016/j.amepre.2009.12.022

12. Nagel R. Severity, Pathobiology, Epistatic Effects, and Genetic Markers in Sickle Cell Anemia. *Semin Hematol*. 1991;28(3):180-201.

13. Modell B, Darlison M. Global Epidemiology of Haemoglobin Disorders and Derived Service Indicators. *Bull World Health Organ*. 2008;86(6):480-487. doi:10.2471/BLT.06.036673

14. Weatherall DJ. The Inherited Diseases of Hemoglobin Are an Emerging Global Health Burden. *Blood*. 2010;115(22):4331-4336. doi:10.1182/blood-2010-01-251348

15. Edoh D, Antwi-Bosaiko C, Amuzu D. Fetal Hemoglobin during Infancy and in Sickle Cell Adults. *Afr Health Sci*. 2006;6(1):51-54. doi:10.5555/afhs.2006.6.1.51

16. Ingram VM. A Specific Chemical Difference between the Globins of Normal Human and Sickle-Cell Anaemia Haemoglobin. *Nature*. 1956;178(4537):792-794.

17. Vrettou C, Traeger-Synodinos J, Tzetis M, Palmer G, Sofocleous C, Kanavakis E. Real-Time PCR for Single-Cell Genotyping in Sickle Cell and Thalassemia Syndromes as a Rapid, Accurate, Reliable, and Widely Applicable Protocol for Preimplantation Genetic Diagnosis. *Hum Mutat*. 2004;23(5):513-521. doi:10.1002/humu.20022

18. Clinvar. National Center for Bioinformation Technology. https://www.ncbi.nlm.nih.gov/clinvar/?term=hbb%5Bgene%5D. Accessed February 11, 2018.

19. Figueiredo MS. The Compound State: Hb S/beta-thalassemia. *Brazilian J Hematol Hemotherapy*. 2015;37(3):150-152. doi:10.1016/j.bjhh.2015.02.008

20. Fanestil V, Van Siclen C. Differentiation between Sickle Cell Anemia and S/β0 Thalassemia. *Lab Med*. 2015;46(3):e79-e81. doi:10.1309/LMKW5VWNUK26LKAX

21. Herrick JB. Peculiar Elongated and Sickle-Shaped Red Blood Corpuscles in a Case of Severe Anemia. *Arch Intern Med*. 1910;5:517-524.

22. Washburn R. Peculiar Elongated and Sickle-Shaped Red Blood Corpuscles in a Case of Severe Anemia. *Virgina Med Semi-Monthly*. 1911;15:490-493.

23. Taliaferro WH, Huck JG. The Inheritance of Sickle-Cell Anaemia in Man. *Genetics*. 1923;8(6):594-598. doi:10.1001/ARCHINTE.1944.00210210032005

24. Sydenstricker V. Sickle Cell Anemia. *South Med J*. 1924;(17):177-183.

25. Huck JG. Sickle Cell Anaemia. *Johns Hopkins Hosp Bull*. 1923;(34):335-344.

26. Neel J. The Inheritance of Sickle Cell Anemia. *Science (80-)*. 1949;(110):64-66.

27. Margolies M. Sickle Cell Anemia: A Composite Study and Survey. *Medicine (Baltimore)*. 1951;(30):357-443.

28. Cooley T, Lee P. The Sickle Cell Phenomenon. *Am J Dis Child*. 1926;3(32):334-340.

29. Pauling L, Itano H, Singer S, Wells I. Sickle Cell Anemia, a Molecular Disease. *Science (80-)*. 1949;110(2865):543-548.

30. Ingram VM. Abnormal Human Haemoglobins. I. The Comparison of Normal Human and Sickle-Cell Haemoglobins by "Fingerprinting." *Biochim Biophys Acta*. 1958;28:539-545. doi:10.1016/S0022-2836(66)80052-9

31. Overview: Sickle Cell Disease Association of America. Sickle Cell Disease Association of America. https://www.sicklecelldisease.org/about/overview/. Published 2016. Accessed February 12, 2018.

32. Siddiqi A, Jordan LB, Parker CS. Sickle Cell Disease - The American Saga. *Ethn Dis*. 2013;23(2):245-248.

33. Manley A. Legislation and Funding for Sickle Cell Services, 1972-1982. *Am J Pediatr Hematol Oncol*. 1984;6(1):67-71.

34. Peters G, Woolley J. Richard Nixon: Statement on Signing the National Sickle Cell Anemia Control Act. The American Presidency Project. http://www.presidency.ucsb.edu/ws/?pid=3413. Published 1972. Accessed February 12, 2018.

35. Ndefo UA, Maxwell AE, Nguyen H, Chiobi TL. Pharmacological Management of Sickle Cell Disease. *P T A Peer-Reviewed J Formul Manag*. 2008;33(4):238-243.

36. Sickle Cell Disease Research, Surveillance, Prevention, and Treatment Act of 2018, S.2465, 115th Cong. (2017-2018). https://www.congress.gov/bill/115th-congress/senate-bill/2465. Accessed May 16, 2018.

37. Smith LA. Sickle Cell Disease: A Question of Equity and Quality. *Pediatrics*. 2006;117(5):1763-1770. doi:10.1542/peds.2005-1611

38. Strouse J, Lobner K, Lanzkron S, MHS, Haywood C. NIH and National Foundation Expenditures for Sickle Cell Disease and Cystic Fibrosis are Associated with Pubmed Publications and FDA Approvals. Strouse JJ, ed. *Blood*. 2013;122(21):1739.

39. Types of Bleeding Disorders: Hemophilia A. National Hemophilia Foundation. https://www.hemophilia.org/Bleeding-Disorders/Types-of-Bleeding-Disorders/Hemophilia-A. Published 2018. Accessed May 29, 2018.

40. Samuel L. Global Push Gives Hemophilia Patients in Developing World Access to Vital Drug. *Stat*. https://www.statnews.com/2016/04/06/hemophilia-donation-biogen/. Published 2016. Accessed May 29, 2018.

41. FDA Approved Drugs for Hematology. CenterWatch. https://www.centerwatch.com/drug-information/fda-approved-drugs/therapeutic-area/6/hematology. Published 2018. Accessed May 29, 2018.

42. Care: Find a CF Care Center. Cystic Fibrosis Foundation. https://www.cff.org/Care-Centers/Find-a-CF-Care-Center/. Published 2018. Accessed May 17, 2018.

43. Sickle Cell Disease - National Resource Directory. Centers for Disease Control and Prevention. https://www.cdc.gov/ncbddd/sicklecell/map/map-nationalresourcedirectory.html. Published 2017. Accessed March 19, 2018.

44. Grosse SD, Schechter MS, Kulkarni R, Lloyd-Puryear MA, Strickland B, Trevathan E. Models of Comprehensive Multidisciplinary Care for Individuals in the United States with Genetic Disorders. *Pediatrics*. 2009;123(1):407-412. doi:10.1542/peds.2007-2875

45. Telefair J, Myers J, Drezner S. Does Race Influence the Provision of Care to Persons with Sickle Cell Disease?: Perceptions of Multidisciplinary Providers. *J Health Care Poor Underserved*. 1998;9(2):184-195.

46. Watson MS, Mann MY, Lloyd-Puryear MA, Rinaldo P, Howell RR. Newborn Screening: Toward a Uniform Screening Panel and System - Executive Summary. *Genet Med*. 2006;8 Suppl 1(5). doi:10.1097/01.gim.0000223891.82390.ad

47. Guthrie R. The Origin of Newborn Screening. *Screen J Int Soc Neonatal Screen*. 1992;1:5-15.

48. Wilson J, Jungner G. Principles and Practice of Screening for Disease. *Public Health Pap*. 1968;(34). http://apps.who.int/iris/bitstream/10665/37650/17/WHO_PHP_34.pdf.

49. Therrell BL, Adams J. Newborn Screening in North America. *J Inherit Metab Dis*. 2007;30(4):447-465. doi:10.1007/s10545-007-0690-z

50. American Academy of Pediatrics Newborn Screening Task Force. Newborn Screening: A Blueprint for the Future - A Call for a National Agenda on State Newborn Screening Programs. *Pediatrics*. 2000;106(2):389-422. doi:10.1016/s0022-3476(05)83375-x

51. Advisory Committee on Heritable Disorders in Newborns and Children: Recommended Uniform Screening Panel. U.S. Department of Health and Human Services. https://www.hrsa.gov/advisory-committees/heritable-disorders/rusp/index.html. Published 2018. Accessed February 13, 2018.

52. Gaston M, Verter J, Wood G, et al. Prophylaxis with Oral Penicillin in Children with Sickle Cell Anemia. *N Engl J Med*. 1986;314(25):1593-1599.

53. Davis LR. Changing Blood Picture in Sickle-Cell Anaemia from Shortly after Birth to Adolescence. *J Clin Pathol*. 1976;29(10):898-901.

54. Newborn Screening for Sickle Cell Disease and Other Hemoglobinopathies. *J Am Med Assoc*. 1987;258(9):1205-1209.

55. Therrell B, Johnson A, Williams D. Status of NBS Programs in the United States. *Pediatrics*. 2006;117(Supplement 3):S212–S252.

56. Raphael J, Kavanagh P, Wanger C, Mueller B, Zuckerman B. Translating Scientific Advances to Improved Outcomes for Children with Sickle Cell Disease: A Timely Opportunity. *Pediatr Blood Cancer*. 2011;56(7):1005-1008.

57. Newborn Screening Provider Manual for the Commonweath of Pennsylvania. Pennsylvania Department of Health. http://www.health.pa.gov/My Health/Infant and Childrens Health/Newborns and Infants/Documents/859055-NEW-NewbornScreeningProviderManual.pdf. Published 2009. Accessed February 14, 2018.

58. Pennsylvania Newborn Screening and Follow-Up Program. Pennsylvania Department of Health. http://www.health.pa.gov/My Health/Infant and Childrens Health/Newborns and Infants/Pages/Newborn-Screening-and-Follow-Up-Homepage.aspx#.Wvw7VhMvzOR. Published 2018. Accessed May 26, 2018.

59. Grant Agreement for Hemoglobinopathy Newborn Screening. *Pennsylvania Dep Heal*. 2016. doi:10.1109/TDEI.2009.5211872

60. Division of Newborn Screening and Genetics Hemoglobin Trait Map. Pennsylvania Department of Health.

61. Sickle Cell Disease: Complications and Treatment. Centers for Disease Control and Prevention. https://www.cdc.gov/ncbddd/sicklecell/treatments.html. Published 2017. Accessed March 2, 2018.

62. Manci EA, Culberson DE, Yang Y, Gardner TM, Powell R, Haynes Jr J et al. Causes of Death in Sickle Cell Disease: An Autopsy Study. *Br J Haematol*. 2003;123:359-365. doi:4594 [pii]

63. Sickle Cell Disease: Splenic Sequestration. Indiana Hemophilia and Thrombosis Center, Inc. http://www.ihtc.org/patient/blood-disorders/sickle-cell-disease/splenic-sequestration/. Published 2012. Accessed March 3, 2018.

64. Quinn CT. Sickle Cell Disease in Childhood. *Pediatr Clin North Am*. 2013;60(6):1363-1381. doi:10.1016/j.pcl.2013.09.006

65. Ohene-Frempong K, Weiner SJ, Sleeper L a, et al. Cerebrovascular Accidents in Sickle Cell Disease: Rates and Risk Factors. *Blood*. 1998;91(1):288-294.

66. Bernaudin F, Verlhac S, Arnaud C, et al. Impact of Early Transcranial Doppler Screening and Intensive Therapy on Cerebral Vasculopathy Outcome in a Newborn Sickle Cell Anemia Cohort. *Blood*. 2011;117(4):1130-1140. doi:10.1182/blood-2010-06-293514

67. Adams RJ, McKie VC, Hsu L, et al. Prevention of a First Stroke by Transfusions in Children with Sickle Cell Anemia and Abnormal Results on Transcranial Doppler Ultrasonography. *N Engl J Med*. 1998;339(1):5-11. doi:10.1056/NEJM199807023390102

68. Adams R, McKie V, Nichols F, et al. The Use of Transcranial Ultrasonography to Predict Stroke in Sickle Cell Disease. *N Engl J Med*. 1992;326(9):605-610.

69. Hamideh D, Alvarez O. Sickle Cell Disease Related Mortality in the United States (1999-2009). *Pediatr Blood Cancer*. 2009;60:1482-1486.

70. Quinn CT, Rogers ZR, Buchanan GR. Survival of Children with Sickle Cell Disease. *Cell*. 2004;103(11):4023-4027. doi:10.1182/blood-2003-11-3758.An

71. Blinder M, Vekeman F, Sasane M, Trahey A, Paley C, Duh M. Age-Related Treatment Patterns in Sickle Cell Disease Patients and the Associated Sickle Cell Complications and Healthcare Costs. *Pediatr Blood Cancer*. 2013;60:828-835. doi:10.1002/pbc

72. Brousseau DC, Owens P, Mosso A, Panepinto J, Steiner C. Acute Care Utilization and Rehospitalizations for Sickle Cell Disease. *J Am Med Assoc*. 2010;303(13):1288. doi:10.1001/jama.2010.378

73. Sobota AE, Umeh E, Mack JW. Young Adult Perspectives on a Successful Transition from Pediatric to Adult Care in Sickle Cell Disease. *J Hematol Res*. 2015;2(1):17-24. doi:10.12974/2312-5411.2015.02.01.3.

74. Charache S, Terrin ML, Moore RD, et al. Effect of Hydroxyurea on the Frequency of Painful Crises in Sickle Cell Anemia. *N Engl J Med*. 1995;332(20):1317-1322. doi:10.1056/NEJM199505183322001

75. Multicenter Study of Hydroxyurea in Patients With Sickle Cell Anemia (MSH). U.S. National Library of Medicine. https://www.clinicaltrials.gov/ct2/show/NCT00000586. Published 2016. Accessed March 2, 2018.

76. Goldberg M, Brugnara C, Dover G, Schapira L, Charache S, Bunn H. Treatment of Sickle Cell Anemia with Hydroxyurea and Erythropoietin. *N Engl J Med*. 1990;323(6):366-372.

77. Agrawal RK, Patel RK, Shah V, Nainiwal L, Trivedi B. Hydroxyurea in Sickle Cell Disease: Drug Review. *Indian J Hematol Blood Transfus*. 2014;30(2):91-96. doi:10.1007/s12288-013-0261-4

78. Approved Drugs: FDA Approves Hydroxyurea for Treatment of Pediatric Patients with Sickle Cell Anemia. U.S. Food and Drug Administration.

https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm590096.htm. Published 2017. Accessed March 18, 2018.

79. Kinney TR, Helms RW, O'Branski EE, Ohene-Frempong K, Wang W, Daeschner C, Vichinsky E, Redding-Lallinger R, Gee B, Platt OS WR. Safety of Hydroxyurea in Children with Sickle Cell Anemia: Results of the HUG-KIDS Study, a Phase I/II Trial. *Blood*. 1999;94(5):1550-1554.

80. Thornburg CD, Files BA, Luo Z, et al. Impact of Hydroxyurea on Clinical Events in the BABY HUG Trial. *Blood*. 2012;120(22):4304-4310. doi:10.1182/blood-2012-03-419879

81. European Sickle Cell Disease Cohort - Hydroxyurea (ESCORT-HU). U.S. National Library of Medicine. https://www.clinicaltrials.gov/ct2/show/record/NCT02516579?term=NCT02516579&rank =1. Published 2018. Accessed March 18, 2018.

82. Gulbis B, Haberman D, Dufour D, et al. Hydroxyurea for Sickle Cell Disease in Children and for Prevention of Cerebrovascular Events: The Belgian Experience. *Blood*. 2005;105(7):2685-2690. doi:10.1182/blood-2004-07-2704

83. Zimmerman SA, Schultz WH, Davis JS, Pickens CV, Mortier NA, Howard TA et al. Sustained Long-Term Hematologic Efficacy of Hydroxyurea at Maximum Tolerated Dose in Children with Sickle Cell Disease. *Blood*. 2004;103(6):2039-2045. doi:10.1182/blood-2003-07-2475.Reprints

84. Stettler N, McKiernan CM, Melin CQ, Adejoro OO, Walczak NB. Proportion of Adults with Sickle Cell Anemia and Pain Crises Receiving Hydroxyurea. *J Am Med Assoc*. 2015;313(16):1671-1672. doi:10.1001/jama.2015.3075

85. Approved Drugs: FDA Approved L-glutamine Powder for the Treatment of Sickle Cell Disease. U.S. Food and Drug Administration. https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm566097.htm. Published 2017. Accessed March 3, 2018.

86. How Does Endari Work to Treat Sickle Cell Disease? https://www.drugs.com/answers/endari-work-treat-sickle-cell-disease-3323440.html. Published 2017. Accessed March 4, 2018.

87. Niihara Y, Zerez CR, Akiyama DS, Tanaka KR. Oral L-glutamine Therapy for Sickle Cell Anemia: I. Subjective Clinical Improvement and Favorable Change in Red Cell NAD Redox Potential. *Am J Hematol*. 1998;58(2):117-121.

88. A Phase III Safety and Efficacy Study of L-Glutamine to Treat Sickle Cell Disease or Sickle βo-thalassemia. U.S. National Library of Medicine. https://www.clinicaltrials.gov/ct2/show/NCT01179217?term=endari&cond=Sickle+Cell+ Disease&rank=1. Published 2018. Accessed March 4, 2018.

89. Highlights of Prescribing Information. U.S. Food and Drug Administration. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/208587s000lbl.pdf. Published 2017. Accessed March 4, 2018.

90. Iannone R, Ohene-Frempong K, Fuchs EJ, Casella JF, Chen AR. Bone Marrow Transplantation for Sickle Cell Anemia: Progress and Prospects. *Pediatr Blood Cancer*. 2005;44:436-440. doi:10.1002/pbc.20169

91. Find a Donor: HLA Matching. National Marrow Donor Program. https://bethematch.org/patients-and-families/before-transplant/find-a-donor/hla-matching/. Published 2018. Accessed March 4, 2018.

92. Mentzer W, Heller S, Pearle P, Hackney E, Vichinsky E. Availability of Related Donors for Bone Marrow Transplantation in Sickle Cell Anemia. *Am J Pediatr Hematol Oncol*. 1994;16(1):27-29.

93. BMT and Sickle Cell Disease. U.S. National Library of Medicine. https://clinicaltrials.gov/ct2/results?cond=Sickle+Cell+Disease&term=bmt&cntry=&state=&city=&dist=. Published 2018. Accessed May 29, 2018.

94. Hoban MD, Orkin SH, Bauer DE. Genetic Treatment of a Molecular Disorder: Gene Therapy Approaches to Sickle Cell Disease. *Blood*. 2016;127(7):839-848. doi:10.1182/blood-2015-09-618587

95. Pawliuk R, Westerman KA, Fabry ME, Payen E, Tighe R, Bouhassira EE, Acharya SA, Ellis J, London IM, Eaves CJ, Humphries RK, Beuzard Y, Nagel R LP. Correction of Sickle Cell Disease in Transgenic Mouse Models by Gene Therapy. *Science (80-)*. 2001;294(5550):2368-2371. doi:10.1126/science.1065806

96. Ribeil J-A, Hacein-Bey-Abina S, Payen E, et al. Gene Therapy in a Patient with Sickle Cell Disease. *N Engl J Med*. 2017;376(9):848-855. doi:10.1056/NEJMoa1609677

97. ClinicalTrials.gov. U.S. National Library of Medicine. https://www.clinicaltrials.gov/ct2/home. Published 2018. Accessed March 4, 2018.

98. The Lancet Haematology. Gene Therapy for Sickle Cell Disease. *Lancet Haematol*. 2016;3(10):e446. doi:10.1016/S2352-3026(16)30130-2

99. Bourzac K. Erasing Sickle-Cell Disease. *Nature*. 2017;549:S28-S30.

100. Blum RW., Garell D, Hodgman C., et al. Transition from Child-Centered to Adult Heath-Care Systems for Adolescents with Chronic Conditions: A Position Paper for the Society for Adolescent Medicine. *J Adolesc Heal*. 2003;14(7):570-576.

101. Pai AL, Schwartz LA. Introduction to the Special Section: Health Care Transitions of Adolescents and Young Adults with Pediatric Chronic Conditions. *J Pediatr Psychol*. 2011;36(2):129-133. http://www.ncbi.nlm.nih.gov/pubmed/21118867.

102. Annunziato RA, Emre S, Shneider B, Barton C, Dugan CA, Shemesh E. Adherence and Medical Outcomes in Pediatric Liver Transplant Recipients Who Transition to Adult Services. *Pediatr Transplant*. 2007;11(6):608-614. doi:10.1111/j.1399-3046.2007.00689.x

103. American Academy of Pediatrics. A Consensus Statement on Health Care Transitions for Young Adults. *Pediatrics*. 2002;110(6):1304-1306. doi:10.1542/peds.110.6.S1.1304

104. American Academy of Pediatrics. Supporting the Health Care Transition from Adolescence to Adulthood in the Medical Home. *Pediatrics*. 2011;128(1):182-200. doi:10.1542/peds.2011-0969

105. Gray WN, Schaefer MR, Resmini-Rawlinson A, Wagoner ST. Barriers to Transition from Pediatric to Adult Care: A Systematic Review. *J Pediatr Psychol*. 2017;(February):1-15. doi:10.1093/jpepsy/jsx142

106. Rutishauser C, Akré C, Surìs JC. Transition from Pediatric to Adult Health Care: Expectations of Adolescents with Chronic Disorders and their Parents. *Eur J Pediatr*. 2011;170(7):865-871. doi:10.1007/s00431-010-1364-7

107. Agarwal S, Garvey K, Raymond J, Schutta M. Perspectives on Care for Young Adults with Type 1 Diabetes Transitioning from Pediatric to Adult Health Systems: A National Survey of Pediatric Endocrinologists. *Pediatr Diabetes*. 2017;18(7):524-531. doi:10.1007/s10549-015-3663-1.Progestin

108. Lotstein DS, Ghandour R, Cash A, McGuire E, Strickland B, Newacheck P. Planning for Health Care Transitions: Results from the 2005-2006 National Survey of Children With Special Health Care Needs. *Pediatrics*. 2009;123(1):e145-e152. doi:10.1542/peds.2008-1298

109. Vijayan T, Benin AL, Wagner K, Romano S, Andiman WA. Transitioning Care of Adolescents with Perinatally Acquired HIV Infection from Pediatrics to Internal Medicine. *AIDS Care - Psychol Socio-Medical Asp AIDS/HIV*. 2009;21(10):1222-1229. doi:10.1080/09540120902730054

110. Zhou H, Roberts P, Dhaliwal S, Della P. Transitioning Adolescent and Young Adults with Chronic Disease and/or Disabilities from Paediatric to Adult Care Services – An Integrative Review. *J Clin Nurs*. 2016;25(21-22):3113-3130. doi:10.1111/jocn.13326

111. Stollon NB, Paine CW, Lucas MS, et al. Transitioning Adolescents and Young Adults with Sickle Cell Disease from Pediatric to Adult Healthcare: Provider Perspectives. *J Pediatr Hematol Oncol*. 2016;37(8):577-583. doi:10.1097/MPH.0000000000000427.Transitioning

112. Richmond N, Tran T, Berry S. Receipt of Transition Services within a Medical Home: Do Racial and Geographic Disparities Exist? *Matern Child Health J*. 2011;15(6):742-752. doi:10.1007/s10995-010-0635-2

113. Amaral S, Patzer R. Disparities, Race/Ethnicity and Access to Pediatric Kidney Transplantation. *Curr Opin Nephrol Hypertens*. 2013;22(3).

114. Sobota A, Neufeld E, Sprinz P, Heeney M. Transition from Pediatric to Adult Care for Sickle Cell Disease: Results of a Survey of Pediatric Providers. *Am J Hematol*. 2011;86(6):512-515. doi:10.1002/ajh.22006

115. Braun V, Clarke V. Using Thematic Analysis in Psychology. *Qual Res Psychol*. 2006;3(2):77-101. doi:10.1191/1478088706qp063oa

116. Richards L, Morse J. Coding. In: *README FIRST for a User's Guide to Qualitative Methods*. Second. Sage Publications, Inc.; 2007:133-151.

117. About Us: History of the Children's Sickle Cell Foundation, Inc. Children's Sickle Cell Foundation, Inc. http://cscfkids.org/about-us/history. Published 2018. Accessed May 18, 2018.

118. Transitioning to Adulthood. Children's Sickle Cell Foundation, Inc. http://cscfkids.org/living-with-sickle-cell/transitioning-to-adulthood. Published 2018. Accessed June 11, 2018.

119. Musgrove LE. Transition Together: A Study of Pediatric Patients with Sickle Cell Disease As They Transition to Adult Health Care. 2015.

120. Porter JS, Wesley KM, Zhao MS, Rupff RJ, Hankins JS. Pediatric to Adult Care Transition: Perspectives of Young Adults with Sickle Cell Disease. *J Pediatr Psychol*. 2017;42(9):1016-1027. doi:10.1093/jpepsy/jsx088

121. Treadwell M, Telfair J, Gibson RW, Johnson S, Osunkwo I. Transition from Pediatric to Adult Care in Sickle Cell Disease: Establishing Evidence-Based Practice and Directions for Research. *Am J Hematol*. 2011;86(1):116-120. doi:doi:10.1002/ajh.21880

122. Centers for Disease Control and Prevention. Core Functions of Public Health and How They Relate to the 10 Essential Services. U.S. Department of Health and Human Services. https://www.cdc.gov/nceh/ehs/ephli/core_ess.htm. Published 2011. Accessed June 19, 2018.

123. Quinn CT. Clinical Severity in Sickle Cell Disease: The Challenges of Definition and Prognostication. *Exp Biol Med*. 2016;241(7):679-688. doi:10.1177/1535370216640385

124. Lanzkron S, Carroll C, Haywood Jr. C. The Burden of Emergency Department Use for Sickle Cell Disease: An Analysis of the National Emergency Department Sample Database. *Am J Hematol*. 2010;85(10):797-799. doi:10.1002/ajh.21807.The

125. Singh A, Yan K, Brandow A, Panepinto J. Longitudinal Trend in Emergency Department Reliance for Pain among Sickle Cell Disease Patients in Wisconsin. *Blood*. 2017;130(Suppl 1).

126. Yusuf HR, Atrash HK, Grosse SD, Parker CS, Grant AM. Emergency Department Visits Made by Patients with Sickle Cell Disease: A Descriptive Study, 1999-2007. *Am J Prev Med*. 2010;38(40):S536-S541. doi:10.1016/j.amepre.2010.01.001

127. Shankar SM, Arbogast PG, Mitchel E, Cooper WO, Wang WC, Griffin MR. Medical care Utilization and Mortality in Sickle Cell Disease: A Population-Based Study. *Am J Hematol*. 2005;80(4):262-270. doi:10.1002/ajh.20485

128. Strouse JJ, Heeney MM. Hydroxyurea for the Treatment of Sickle Cell Disease: Efficacy, Barriers, Toxicity, and Management in Children. *Pediatr Blood Cancer*. 2012;59(2):365-371. doi:10.1002/pbc.24178

129. Luchtman-Jones L, Pressel S, Hilliard L, et al. Effects of Hydroxyurea Treatment for Patients with Hemoglobin SC Disease. *Am J Hematol*. 2016;91(2):238-242. doi:10.1002/ajh.24255

130. Creary S, Chisolm D, Koch T, Zigmont V, Lu B, O'Brien S. Hydroxyurea Use in Children with Sickle Cell Disease: Do Severely Affected Patients Use It and Does It Impact Hospitalization Outcomes? *Pediatr Blood Cancer*. 2016;63(5):844-847. doi:doi:10.1002/pbc.25894

131. Anders DG, Tang F, Ledneva T, et al. Hydroxyurea Use in Young Children with Sickle Cell Anemia in New York State. *Am J Prev Med*. 2016;51(1):S31-S38. doi:10.1016/j.amepre.2016.01.001

132. Brandow A, Jirovec D, Panepinto J. Hydroxyurea in Children with Sickle Cell Disease: Practice Patterns and Barriers to Utilization. *Am J Hematol*. 2010;6(8):247-253.

133. Zumberg MS, Reddy S, Boyette RL, Schwartz RJ, Konrad TR, Lottenberg R. Hydroxyurea Therapy for Sickle Cell Disease in Community-Based Practices: A Survey of Florida and North Carolina Hematologists/Oncologists. *Am J Hematol*. 2005;79(2):107-113. doi:10.1002/ajh.20353

134. Brandow A, Panepinto J. Hydroxyurea Use in Sickle Cell Disease: The Battle with Low Rates of Prescription, Poor Patient Compliance and Fears of Toxicities and Side Effects. *Expert Rev Hematol*. 2013;3(3):255-260. doi:10.1586/ehm.10.22.Hydroxyurea

135. Quarmyne M-O, Dong W, Theodore R, et al. Hydroxyurea Effectiveness in Children and Adolescents with Sickle Cell Anemia: A Large Retrospective, Population-Based Cohort. *Am J Hematol*. 2017;92(1):77-81.

136. Lanzkron S, Haywood Jr. C, Segal J, Dover GJ. Hospitalization Rates and Costs of Care of Patients with Sickle-Cell Anemia in the State of Maryland in the Era of Hydroxyurea. *Am J Hematol*. 2006;81:927-932.

137. Voskaridou E, Christoulas D, Bilalis A, et al. The Effect of Prolonged Administration of Hydroxyurea on Morbidity and Mortality in Adult Patients with Sickle Cell Syndromes: Results of a 17-Year, Single-Center Trial (LaSHS). *Blood*. 2010;115(12):2354-2363. doi:10.1182/blood-2009-05-221333