

SICKLE CELL TRAIT COUNSELING FOR STUDENT ATHLETES

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University of Pittsburgh, 2011

Objectives: In April 2010, the National Collegiate Athletic Association (NCAA) approved mandatory testing for sickle cell trait status for all student athletes participating in Division I sports. Children's Sickle Cell Program at Children's Hospital of Pittsburgh offered genetic testing and counseling to all student athletes participating in Division I athletes at the University of Pittsburgh and Duquesne University.

Methods: To assess the knowledge of sickle cell trait among the student athletes, along with the effect of genetic counseling, student athletes were asked to participate in a survey. A short survey was provided to the student athletes prior to their genetic counseling, with a short survey provided following the genetic testing (See Appendix A for IRB consent form and Appendix B for questionnaires).

Results: Between the two Division I programs at the University of Pittsburgh and Duquesne University, 122 student athletes were tested of which, one athlete was diagnosed with sickle cell trait. Among the 122 student athletes tested, 80 participated in the surveys. Among those who participated, 57 (71%) were Caucasian, 16 (20%) were African American, and the remaining athletes were of mixed or other ethnic backgrounds. Prior to the genetic counseling session, 11% of the student athletes answered that they had never heard of sickle cell disease or sickle cell trait. Following the genetic counseling session, 89% of the student athletes had a good

understanding of sickle cell trait, with 15% showing that they learned something from the genetic counseling session.

Conclusions: Based on the data obtained from this study, student athletes may not have a good understanding of the testing that is mandated by the NCAA. Therefore, genetic counseling is strongly recommended to all student athletes prior to carrier status testing.

Implications for Public Health: The NCAA has been criticized for their ruling mandating sickle cell trait testing. However, many are not focusing on the importance of the impact genetic testing has on an individual, particularly this age range involved. Genetic counseling needs to be considered when requiring these student athletes to undergo genetic testing for sickle cell trait.

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PREFACE

I would like to thank the faculty of the Graduate School of Public Health, especially those within the Human Genetics Department for their guidance and support. Most importantly Robin Grubs and Betsy Gettig who provided my classmates and I with the knowledge and support to shape us into Genetic Counselors.

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To my fellow classmates, I could not have completed this program without you. I am truly grateful for our friendships and the support we have provided each other these past two years (and hope to continue in the future). Finally to my family, who have supported me all of

my life, even when I decided to change career paths. Your enthusiasm and encouragement through this entire process has given me the confidence to get where I am today. I am fortunate to have such a wonderful and caring family and words cannot express my love for you.

1.0 INTRODUCTION

In the United States, the prevalence of SCT among African Americans is about 8%, or 1 in 12 African Americans. Sickle cell trait, or sickle cell carriers, are characterized by the presence of both Hb A and Hb S, given them the genotype Hb AS. Studies performed over the years have focused on the association between sickle cell trait and exertional exercise. Studies, first from the military, then on athletes across high school and collegiate sports, have demonstrated a link between unexplained sudden death related to exercise and sickle cell trait.

Individuals with sickle cell trait are typically thought of as being asymptomatic with a normal life span. Some studies show that individuals with sickle cell trait may actually be at a slightly increased risk for splenic infarction, exertional rhabdomyolysis, and exercise-related sudden death.¹ It is hypothesized that if an athlete has sickle cell trait, intense exercise can cause changes in the body known to cause sickling, also known as exertional sickling. Exertional sickling can lead to rapid muscle break down, called rhabdomyolysis, which can be fatal.

In April 2010, the National Collegiate Athletic Association (NCAA) approved mandatory testing for sickle cell trait status for all student athletes participating in Division I sports. This was a change from previous years, in which sickle cell trait testing was recommended, and offered on a voluntary basis, at the discretion of individual athletic programs. To accommodate local Pittsburgh, PA universities, including the University of Pittsburgh and Duquesne University, the Children's Sickle Cell Program and Children's Hospital of Pittsburgh offered

genetic testing and counseling to student athletes at the University of Pittsburgh. In an attempt to expand our program, the aim of this study was to extend our contact to other local Pittsburgh universities and offer genetic counseling and testing services to their student athletes. This project was successive in expanding our services to include the University of Pittsburgh and Duquesne University Athletic Departments. Genetic counseling and testing was provided to all student athletes willing to participate. Questionnaires (Appendix B) were administrated to those student athletes willing to participate in that particular part of the study. A pre-counseling questionnaire was offered to the student athletes prior to their counseling session, which contained basic knowledge of sickle cell disease and sickle cell trait. Following the genetic counseling session and the blood test for sickle cell trait, a post-counseling questionnaire was offered to the student athletes, containing similar questions as those found on the pre-counseling questionnaire. The aim of the questionnaires was to gain a better understanding of the prior knowledge of sickle cell disease and sickle cell trait, along with the effectiveness of the genetic counseling provided to the student athletes. Our ultimate goal is to bring awareness of sickle cell trait to the athletic community and emphasize the importance of genetic counseling in association with genetic testing.

2.0 SPECIFIC AIMS

2.1 SPECIFIC AIM 1

Specific Aim I: To provide sickle cell trait testing to student athletes.

The first aim of this study was to provide sickle cell trait testing to student athletes participating in Division I sports teams at the University of Pittsburgh and Duquesne University. Compliance with the NCAA ruling passed in April 2010, and effective August 2010 was followed to allow for timely and effective testing of student athletes.

2.2 SPECIFIC AIM 2

Specific Aim 2: To provide counseling and education to student athletes on sickle cell trait and the potential complications associated with sickle cell trait in athletes.

The second aim of this study was to provide genetic counseling and education to student athletes prior to undergoing genetic testing for sickle cell trait. Counseling and education material were aimed at the proposed physiology of exertional sickling related to sickle cell trait in athletes along with the signs and symptoms and forms of prevention.

2.3 SPECIFIC AIM 3

Specific Aim 3: To survey the student athletes in order to obtain information and evaluate the counseling offered along with the impact the new NCAA ruling has on the student athletes.

The third aim of this study was to provide the student athletes with questionnaires prior to and following genetic counseling and genetic testing for sickle cell trait. This aim was to assess the general knowledge of sickle cell disease and sickle cell trait. This aim was also to obtain the effectiveness of the genetic counseling along with the experience of undergoing genetic counseling and genetic testing in the athletic setting.

3.0 BACKGROUND AND SIGNIFICANCE

In humans, hemoglobin is a globular protein molecule¹ comprised of alpha and beta globin chains. The α -globin chain is located on chromosome 16 and codes for the adult α -globin and the ζ -globin chain, which is the embryonic form of α -globin. The β -globin chain is located on chromosome 11. At this location, four genes are present, which include the embryonic ϵ gene, the fetal γ gene, the adult δ gene, and the adult β gene.¹ These four types of hemoglobin are expressed differently at particular times of our development. Figure 1 demonstrates the timeline of the expression of the human globin genes from the early stages of fetal development to the changes that occur at birth and the first year of life.

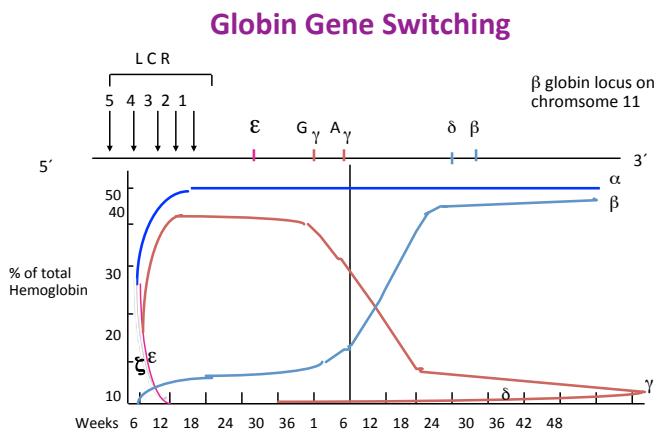


Figure 1: Timeline of the expression of the human globin genes

Over 400 types of hemoglobin exist. The most common hemoglobins include Hb A, Hb A₂, Hb S, Hb C, Hb F, Hb D Punjab (or D Los Angeles), and Hb O Arab⁴ (Table 1).

Table 1: Types of Hemoglobin (Adapted from Serjeant⁴).

Hb A	$\alpha_2\beta_2$
Hb A ₂	$\alpha_2\delta_2$
Hb S	Glutamic acid (GAG) → valine (GTG) at position β^6
Hb C	Glutamic acid (GAG) → lysine (AAG) at position β^6
Hb F	$\alpha_2\gamma_2$
Hb D Punjab (or D Los Angeles)	Glutamic acid (GAG) → glutamine (CAG) at position β^{121}
Hb O Arab	Glutamic acid (GAG) → lysine (AAG) at position β^{121}
HbE	Glutamic acid (GAG) → lysine (AAG) at position β^{26}

3.1 SICKLE CELL DISEASE

Sickle cell disease is an autosomal recessive genetic blood disorder that predominately affects persons of African ancestry.³ However, sickle cell disease can also affect persons of Mediterranean, Caribbean, South and Central American, Arabian, and East Indian ancestry.³ James B. Herrick first described sickle cell disease in 1910, with his identification of abnormally shaped red blood cells, which he identified as sickle-shaped, giving the disease its name.

Sickle cell disease is defined by the presence of Hemoglobin S (Hb S). Sickle Hemoglobin (Hb S) is an example of a single point mutation involving GAG → GTG transversion at codon 6 of the β -globin gene.^{1,4} This single point mutation causes a change in amino acid at position 6 in the β -globin chain from glutamic acid to valine. The position of this change is located on the surface of the hemoglobin molecule. The replacement of glutamic acid with valine results in a change in the characteristics of the deoxygenated Hb S, causing Hb S to become much less soluble than Hb A. When Hb S becomes deoxygenated, polymerization of Hb S occurs in erythrocytes. The polymer takes on the form of an elongated rope-like fiber or rigid tubule,^{5,6,7} causing a change in shape from the smooth, doughnut-shaped red blood cells⁵ to hallmark sickle-shape cells. Sickle-shaped cells are stiff and sticky and can cause blockages in the small blood vessels.⁵ When this occurs, an adequate blood supply may not be able to reach organs and tissues, resulting in damage to these particular organs or tissues.³ The Pathophysiology of sickle cell disease can be illustrated in Figure 2.⁸

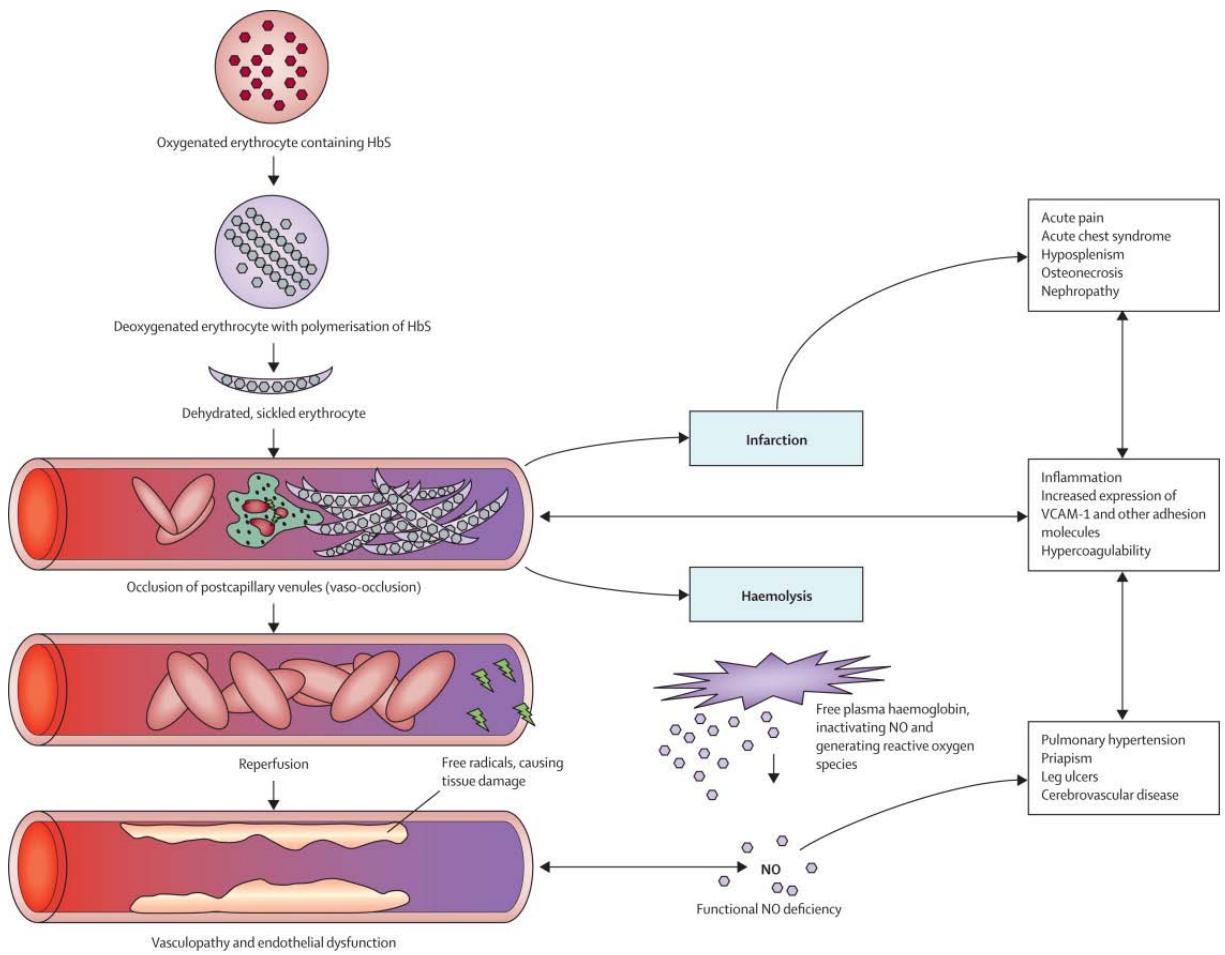


Figure 2: Pathophysiology of sickle-cell disease⁸

Hb SS is the most common form of sickle cell disease and is believed to affect more than 50,000 Americans. Sickle cell disease is most common among individuals of African descent; however, individuals of Mediterranean, Caribbean, South and Central America, Arabian, and East Indian descent may also be affected. The estimated prevalence of Hb SS among African American live births is believed to be one out of every 375 live births, while the estimated prevalence of Hb SC among African American live births is believed to be one out of every 835 live births. Due to the prevalence of sickle cell disease, it is believed that approximately 8% or 1 in 12 of the African American population in the United States carry Hb S, giving them the diagnosis of sickle cell trait.³

Sickle cell disease can also occur when an individual inherits hemoglobin S from one parent and hemoglobin C from the other parent, denoted Hb SC. Hb SC disease is less common than Hb SS disease among the African American population.⁹ Hb C does not participate⁹ in polymerization with deoxygenated Hb;^{10,11} however, the presence of Hb C within the cell does lead to enhanced and sustained potassium and chloride cotransport.¹⁰ The loss of potassium causes the erythrocytes to become dehydrated, which in turn leads to an increased concentration of Hb S erythrocytes.¹⁰ Depending on the levels, polymerization and sickling are likely to occur.

Individuals with Hb SC disease may demonstrate clinical symptoms similar to those seen in Hb SS disease. Some studies demonstrate that the symptoms of Hb SC disease may be less severe than Hb SS. There appears to be much variation among individuals with both Hb SS and Hb SC disease.^{12,13} Individuals with Hb SC disease are at risk for the same life-threatening complications as those with Hb SS disease. Complications may occur less frequently in Hb SC disease than they appear to in Hb SS disease.^{12,13}

3.1.1 Inheritance

Sickle cell disease is an autosomal recessive condition and occurs when an individual inherits an abnormal hemoglobin gene from both parents. If an individual has one sickle cell gene and one normal β^A -chain gene,⁴ they have what is known as sickle cell trait. If both parents have an abnormal hemoglobin gene, in each pregnancy, the couple would have a 25% or 1 in 4 chance of both passing on their abnormal hemoglobin gene, resulting in a child with hemoglobin disease.

3.1.2 Clinical Manifestations

The clinical hallmarks of sickle cell disease include vaso-occlusive phenomena and hemolysis.¹⁴ Vaso-occlusive phenomena, previously known called sickle cell crisis, is the occlusion of a blood vessel,⁸ resulting in recurrent painful episodes. Hemolysis is a variety of serious organ system complications that can lead to life-long disabilities and/or early death.¹⁴ Other complications that are typically associated with sickle cell disease include anemia, dactylitis, acute pain episodes, splenic sequestration, and vaso-occlusion in any organ system.¹⁴

3.1.2.1 Blood

Acute painful episodes, previously called sickle cell crisis, are the most common type of vaso-occlusive event that occurs in sickle cell disease. These episodes are the most frequent symptom individuals with sickle cell disease experience and it is usually the reason individuals seek medical attention.^{1,15,16} There is a great deal of variability among individuals with sickle cell disease when it comes to the severity, frequency, location, and duration of episodes.^{1,17,18} Some studies show that the frequency of episodes may peak around the ages 19-39.¹⁹ These pain

episodes may be triggered by a number of events, including, weather conditions, dehydration, infection, stress, menses, alcohol consumption, nocturnal hypoxemia, and obstructive sleep apnea.²⁰⁻²⁵ Examples of weather conditions that may prompt pain episodes include cold temperatures, high wind speed, low humidity, and atmospheric pollutants.^{1,26-28}

Sickle cell patients experiencing an acute painful episode, tend to experience pain primarily in the upper back (63%) or the left arm (61%).²⁹ Patients with sickle cell disease may also experience pain in their legs (38%), chest (26%), or lower back (12%).²⁹ Individuals experiencing an acute painful episode may exhibit clinical signs, such as a fever, swelling or tenderness in the region of the vaso-occlusion, tachypnea, hypertension, and nausea or vomiting.¹

The majority of individuals with sickle cell disease experience chronic anemia, with varying degrees of severity.¹ The life-long anemia is likely caused by hemolysis,¹ or the destruction of red blood cells.³⁰

3.1.2.2 Spleen

As normal blood enters the spleen through the splenic artery, it must pass through progressively smaller arterial vessels,³⁰ undergoing mechanical stress and physical remodeling.¹ In sickle cell disease, the red blood cells are more rigid and are unable to pass through the splenic sinus gaps,¹ resulting in increased destruction of red blood cells.^{1,30} If there is vaso-occlusion or splenic congestion that continues without resolving on its own, the spleen may become enlarged.¹

Individuals with sickle cell disease may experience splenic involvement, which may be characterized by the following: minimal change; splenomegaly; asplenia or hyposplenism; splenic sequestration crisis; and hypersplenism.¹ Some individuals may not experience any signs or symptoms of an affected spleen, until they are exposed to high altitudes. At this time, they may experience abdominal pain as a result of splenic infarction.¹

Splenomegaly is more commonly seen in children, particularly those under the age of 6 years, compared to adults with sickle cell disease.¹ Splenic sequestration may occur in individuals with splenomegaly, in which the blood becomes trapped in the spleen. Individuals may experience fever, pain and respiratory symptoms. Splenic sequestration may present as splenic enlargement, which is often tender, a drop in hemoglobin concentration of at least 2 g/ dL, thrombocytopenia, and/or reticulocytosis.³¹ Studies have suggested that infants who experience a splenic sequestration episode may experience a second event within 12 months of the initial event.³² Splenic sequestration can be life threatening if left untreated, even for a few hours.

3.1.2.3 Infection

Infection is a major cause of morbidity and mortality in patients with sickle cell disease, with bacterial infection being the most common cause of death in infants and young children with sickle cell disease.¹ Table 2 includes bacteria and viruses that most frequently cause serious infection in patients with sickle cell disease.¹ The most common organism causing infection is pneumococcus and individuals under the age of 3 years are particularly at an increased risk of infection. Due to this knowledge, the initiation of prophylactic penicillin, which pneumococcus is extremely sensitive to,¹ in the first few months of life has been an effective and inexpensive form of treatment in individuals with sickle cell disease.

Table 2: Bacteria and viruses that most frequently cause serious infection in patients with sickle cell disease¹

Microorganism	Type of Infection	Comments
Streptococcus pneumonia	Septicemia	Common despite prophylactic penicillin and pneumococcal vaccine
	Meningitis	Less frequent than in years past
	Pneumonia	Rarely documented except in infants and young children
	Septic arthritis	Uncommon
Hemophilus influenza, type b	Septicemia, meningitis, pneumonia	Much less common in recent years because of immunization with conjugate vaccine
Salmonella species	Osteomyelitis, septicemia	Most common cause of bone and joint infection
Escherichia coli and other Gram-negative enteric pathogens	Septicemia, urinary tract infection, osteomyelitis	Focus sometimes inapparent
Staphylococcus aureus	Osteomyelitis	Uncommon
Mycoplasma pneumonia	Pneumonia	Pleural effusions; multilobe involvement
Chlamydia pneumonia	Pneumonia	
Parvovirus B19	Bone Marrow suppression (aplastic crisis)	High fever common; rash and other organ involvement infrequent
Hepatitis viruses (A, B, and C)	Hepatitis	Marked hyperbilirubinemia

3.1.2.4 Growth and Development

Infants with sickle cell disease are born within normal weight and length and their early growth appears to be normal as well. As time progresses, the mean height and weight of individuals with sickle cell disease may drop below the 50th percentile, particularly by the age of 2 years. As children age, these growth deficits may become progressively more pronounced.¹ Studies have shown that an individual's weight is more severely affected than height.^{1,34}

Individuals with sickle cell disease may also experience delays in sexual maturation. Females with sickle cell disease may experience a delay in the onset of menarche and the progression through Tanner stages of development.¹ Males with sickle cell disease also experience delays in the progression through Tanner stages of development along with lower levels of testosterone, dihydrotestosterone, and androsteneion.¹

3.1.2.5 Neurological

Studies show that 24% of individuals with sickle cell disease may experience a form of neurologic injury, with the major cause being associated with cerebrovascular disease.¹ Cerebrovascular disease may present as cerebral infarction or intracranial hemorrhage. Young individuals with sickle cell disease are predisposed to stroke, and may experience a stroke following a pain crisis, infection, or other systemic illness.¹ Although it may occur following these events, it is uncertain if these events are causative. A form of stroke, known as ischemic stroke, is common in individuals with sickle cell disease and is caused by oxygen deprivation due to occlusion of blood vessels.¹ Individuals who experience stroke typically make a good recovery of motor function yet, they may experience some cognitive deficits.¹ An intracranial hemorrhage may destroy the brain as a result of direct trauma from arterial jets of blood, by delayed vasospasm causing arterial narrowing that can produce infarction, or by compression of normal tissue by mass effect.¹

Individuals with sickle cell disease may also experience other neurological injury, such as hearing loss, neuropathy, or cognitive dysfunction. The cause of hearing loss is currently unknown, but may be a result of vascular compromise.¹ Neuropathy may present as mental nerve lesions causing numbness of the chin.¹

3.1.2.6 Bone

Individuals with sickle cell disease may experience bone and joint concerns, primarily due to a limited blood supply to the region. Bone complications may include bone infarction or osteomyelitis.¹ Bone infarctions may occur in the long bones, leading to swelling and tenderness localized to the area.¹ An example of this is dactylitis in early childhood, also known as the “hand-foot syndrome.”¹ This syndrome is typically the first manifestation seen in infants with

sickle cell disease between the ages of six months and two years.¹ These infants experience infarctions in the small long bones of the hands and feet, causing painful swelling of the hands and feet.¹

Some individuals with sickle cell disease may also present with osteomyelitis, an acute or chronic bone infection, most often caused by salmonellae.¹ Bone infarctions and osteomyelitis may present similar and may be difficult to distinguish.¹ The onset of symptoms may assist with distinguishing, with infarctions beginning more acutely, while osteomyelitis may have a more prolonged onset.¹

3.1.2.7 Pulmonary

Individuals with sickle cell disease may present with a variety of chronic manifestations including restrictive and obstructive lung disease, hypoxemia, pulmonary hypertension, airway hyperreactivity, asthma, or sleep-related upper airway obstruction.³⁵⁻³⁷ Pulmonary complications may present as acute or chronic disorders.¹

The most common acute complication seen in individuals with sickle cell disease is acute chest syndrome, occurring in 15-43% of affected individuals.¹ Acute chest syndrome occurs as a result of vascular occlusion or infection in the lungs.³⁰ Individuals experiencing acute chest syndrome may experience chest pain, tachypnea, fever, rales and rhonchi, leukocytosis, or lobar consolidations.³⁰

3.1.2.8 Renal

In a typical kidney, an average of 4-8% of the body's total oxygen is consumed to assist in the elevated metabolic activity performed by the tubules.¹ One of the main renal complications seen in individuals with sickle cell disease is occlusion of the vasarecta capillaries in the renal

medulla,³⁸ leading to a change in the delivery of oxygen to the kidney,¹ which in turn leads to ischemic damage.¹

The most prevalent clinical manifestation of sickle cell renal disease is hematuria, which may occur as a consequence of papillary infarcts or necrosis.^{1,38} Hematuria has been seen in individuals with sickle cell disease, along with those with sickle cell trait.¹ Bleeding occurs primarily from the left kidney; however, it has occurred bilaterally in rare cases.¹ Hematuria may be painless³⁸ and can be diagnosed by the use of radiography.¹

Additional clinical manifestations seen in individuals with sickle cell disease include proteinuria and hypertension; renal infarction, papillary necrosis, and renal colic; nephrogenic diabetes insipidus that can lead to polyuria; focal segmental glomerulosclerosis that can lead to end-stage renal disease; and renal medullary carcinoma.³⁸ End-stage renal disease may occur in 4-18% of individuals with sickle cell disease,¹ Dialysis seems to be well tolerated by these individuals and there have been an increasing number of patients over the years that are now being treated with renal transplantation.³⁸

3.1.2.9 Ophthalmologic

Individuals with sickle cell disease may experience ophthalmologic complications as a result of erythrocyte sickling, which can occur in any microvascular bed of the eye.¹ Depending on the tissue that is involved and the location of the vaso-occlusion, an individual's vision may or may not be affected.¹ In individuals who experience ophthalmologic complications, primarily the retina is affected,^{39,40} and they may experience proliferative retinopathy, retinal artery occlusion, or retinal detachment and hemorrhage.^{39,40}

3.1.3 Management

The main objectives in the management of patients with sickle cell disease include prevention and treatment of complications of sickle cell disease.⁴¹ In an attempt to prevent the complications associated with sickle cell disease, the aim is to establish routine follow-up with a comprehensive team, which includes a clinician and a variety of multidisciplinary interventions, such as pharmacological, behavioral, psychological, and physical interventions.⁴²⁻⁴⁴ During routine visits, clinicians should establish steady state values for an individual, to allow for comparison during episodes of complication. Laboratory values such as hemoglobin, white blood count, and pulse oximetry readings can be informative.^{42,43} Routine evaluations should also include neurology, ophthalmology, cardiology, pulmonary, psychological/behavioral, and a general physical evaluation.⁴⁵⁻⁴⁹

Children with sickle cell disease should undergo a transcranial Doppler in order to evaluate the cerebral blood flow. This procedure should be performed at least every 12-24 months beginning at the age of two until a child reaches the age of 16.⁴⁵ Transcranial Dopplers are not required for individuals over the age of 16 years.⁴⁵ Once a child with sickle cell disease becomes of school age, they should undergo retinal evaluation on a routine basis. Starting at the age of 15, individuals with sickle cell disease should undergo an echocardiogram at least every other year.⁴⁶ This recommendation is based on findings indicating an association of elevated tricuspid regurgitant jet velocity evident on echocardiograms with increased mortality.⁴⁶ Pulmonary complications are associated with sickle cell disease; therefore, baseline pulmonary function studies should be performed on individuals with sickle cell disease at least every two years.

Sickle cell disease, being a chronic disease, can have major psychological complications. Due to the clinical manifestations associated with the disease, such as pain episodes and the implication they have on an individual's life, depression can be a significant component of the disease. Pain episodes can also affect everyday life activities, such as school and work; therefore, assistance in these areas may be required. Family planning and birth control counseling may also be discussed in families with a history of sickle cell disease. A routine physical exam is recommended for assessment of bone health by calcium intake, vitamin D status, and bone density at 12 years of age.⁴⁸ A chemistry panel and urinalysis should also be performed twice a year, in an attempt to monitor renal disease, proteinuria, and organ dysfunction.⁴⁹

3.1.3.1 Management of Infection

Bacterial infection is the most common cause of death in infants and young children with sickle cell disease and a significant cause of morbidity in older patients.¹ The highest rates of infection appear to affect younger patients, particularly those under the age of 3.¹ Since we are aware of this risk of infection, and with our ability to diagnosis sickle cell disease by newborn screen in the first few weeks of an infant's life, the administration of penicillin V is initiated within three months of birth.^{50,51} A twice daily oral dose of 125 mg is administrated until the age of 2-3 years, at which time the dose is increased to 250 mg twice daily until the age of 5.^{50,51} After the age of 5, parents may elect to continue or stop treatment. This option is available to parents due to the uncertainty of the benefits and risks of continuing treatment with penicillin V after this age.⁵¹ Regardless of the decision a parent makes, monitoring for fever should continue.⁵²

Children with sickle cell disease should also receive routine vaccinations, including immunization against Streptococcus pneumonia, Haemophilus influenza type B, hepatitis B

virus, and influenza.⁵³⁻⁵⁶ If a child with sickle cell disease encounters a fever, they should undergo an evaluation that includes a physical examination, a complete blood count, blood and urine cultures, and a chest x-ray. If meningitis is suspected, a lumbar puncture should also be performed.

3.1.3.2 Splenic Sequestration

Splenic sequestration may occur in individuals with sickle cell disease, presenting as splenic enlargement, which is often tender, a drop in hemoglobin concentration of at least 2 g/ dL, thrombocytopenia, and/or reticulocytosis.³¹ The primary concern surrounding splenic sequestration is hypovolemic shock.³³ This becomes a concern as a result of a disproportionate amount of intravascular blood volume becoming sequestered in the spleen due to ensnared red and white blood cells.³¹

Management is typically initiated following an initial event. Patients should be educated about self-palpation of the spleen and instructions on what to do in the event of an enlarging spleen.³¹⁻³³ Following an event, individuals with sickle cell disease may contemplate removing the spleen, once they evaluate the risks and benefits of the procedure.³¹⁻³³ Regular blood transfusion therapy may also be considered in an attempt to prevent subsequent episodes of acute splenic episodes; however, the exact benefits of this type of therapy have yet to be proven.³¹⁻³³

3.1.3.3 Pain Management

Acute, painful episodes are the most common cause for sickle cell disease patients to seek medical attention.⁵⁷ The definition for an acute, painful episode may vary depending on the source. The Cooperative Study of Sickle Cell Disease (CSSCD) defined a pain episode as pain related to sickle cell disease in the extremities, back, abdomen, chest or head lasting at least two

hours and leading to a clinic visit or hospitalization.⁵⁷ Studies have shown that the annual incidence rate of pain episodes does increase with age; however, these rates may be greatly underestimated due to the fact that many adults who experience an acute, painful episode do not seek medical attention.⁵⁸ Instead of seeking medical attention, many patients attempt to manage their pain at home. Studies have shown that many adults with sickle cell disease experience pain on almost a daily basis⁵⁸ and manage this pain at home until it exceeds their ability to maintain with oral opioids.⁵⁸

Home management of pain associated with sickle cell disease is similar to the World Health Organization (WHO) guidelines for the treatment of cancer-related pain.⁵⁹ These guidelines use a stepwise approach, by which the therapy is increased as the severity of the pain increases.⁵⁹ Patients with sickle cell disease are recommended to work along with their clinician and multidisciplinary team to create a standard treatment plan for their management at home.

Once a patient with sickle cell disease seeks medical attention, the emergency department should initiate prompt treatment according to the American Pain Society (APS).^{59,60} APS outlines steps to ensure proper and effective treatment of pain once a sickle cell patient is present in an emergency department. A patient's team, to ensure effective treatment and management of pain for that particular patient, may also compose individual pain management plans.

Much effort has been put forth in an attempt to discover therapies that treat severely affected sickle cell disease patients, particularly when it comes to pain management. Hydroxyurea is a therapy used for the overall management of sickle cell disease. Hydroxyurea was FDA-approved in 1998 for the use of severely affected adults with sickle cell disease.⁶¹ Hydroxyurea therapy is believed to reduce hemolysis and vaso-occlusion as a result of the prevention of intracellular sickling.⁶¹ The underlying concept of Hydroxyurea is that it increases

the percentage of fetal hemoglobin.⁶¹ Clinical observations have suggested that increased fetal hemoglobin concentrations have beneficial effects in sickle cell disease,⁶¹ which may be attributed to fetal hemoglobin lacking β-chains.⁶² The process of sickling of the red blood cells is triggered by deoxygenated hemoglobin S, which undergo polymerization and transform into rigid rod-like polymers.⁶² The lack of β-chains inhibits the polymerization of hemoglobin S, decreasing the occurrence of sickling events.

A controlled trial of the efficacy of Hydroxyurea in patients with sickle cell anemia was performed by Charache et al,⁶² which involved 148 males and 151 females across 21 clinics, of which 152 patients were assigned to Hydroxyurea treatment.⁶² This study demonstrated that the treatment with Hydroxyurea caused a 44% reduction in the median annual rate of painful episodes, along with reducing the frequency of chest syndrome and the number of transfusions.⁶² Hydroxyurea has been shown to be effective within two months of beginning treatment, with noticeable differences by four months of use.⁶²

The risks associated with the use of Hydroxyurea is still unclear, particularly use during pregnancy.^{62,63} There is a concern for the long-term use of Hydroxyurea and the risk of cancer, birth defects and leg ulcerations.⁶³ Given the fact that Hydroxyurea blocks the synthesis of DNA by inhibiting ribonucleotide reductase, similar to other antieoplastic agents, the trepidation is that Hydroxyurea may be carcinogenic or leukemogenic.⁶² Sickle cell patients and clinicians must weight out the benefits of Hydroxyurea treatment with the uncertain safety of the long-term Hydroxyurea therapy.⁶²

3.1.3.4 Transfusion Therapy

Transfusion of normal blood in patients with sickle cell disease allows for the addition of normal red blood cells, lowering the percentage of red blood cells containing Hb S.⁶⁴ Exchange transfusion is the process of theoretically replacing Hb S with HbA.⁶⁴ This process involves transfusing normal blood in, while removing other blood.^{8,64} Exchange transfusion is more commonly utilized in individuals with initially high concentrations of Hb S.⁸ In these individuals, a rapid reduction in the Hb S percentage is required, which is ideally achieved through the process of exchange transfusion.⁸ The indications for blood transfusion in sickle cell disease can be found in Table 3.⁸

The benefits of transfusion include the management of acute complications associated with sickle cell disease. These may include acute stroke, acute chest syndrome, acute multi-organ failure, and acute symptomatic anemia. Other complications associated with sickle cell disease, such as splenic sequestration, may also be managed through transfusion therapy. Aside from the evident benefits associated with transfusions, much controversy surrounds chronic transfusion therapy. Risks associated with chronic transfusion therapy include iron overload, transfusion reactions, viral infection, and alloimmunization.⁸ Just as in any type of therapy that carries a risk, the potential benefits need to be weighted against the potential risks, when making management decisions.

Table 3: Indications for blood transfusion in sickle-cell disease⁸

Indications for acute transfusions
Acute exacerbation of anemia
Typically caused by Parvovirus B19 infection, splenic or hepatic sequestration, or severe vaso-occlusion; simple transfusion is necessary to increase hemoglobin concentrations to 80–90 g/L
Acute chest syndrome
Early simple top-up transfusion is beneficial, with exchange transfusion to reduce HbS to less than 30% if deterioration of clinical condition occurs
Stroke or acute neurological deficit
Urgent transfusion to increase hemoglobin concentrations to 100 g/L, and reduce HbS to less than 30%, which typically requires exchange transfusion
Multiorgan failure
HbS to less than 30% with hemoglobin concentration of 100 g/L
Preoperative management
Target HbS of less than 30% before major surgery (cardiothoracic, neurosurgery), typically requiring exchange transfusion; medium-risk or low-risk surgery might need simple transfusion to increase hemoglobin concentration to 100 g/L
Indications for regular, long-term transfusions
Primary and secondary stroke prevention
Regular transfusions, either simple or exchange, to keep HbS less than 30%
Recurrent acute chest syndrome not helped by hydroxycarbamide
Regular transfusions, either simple or exchange, to keep HbS less than 30%
Progressive organ failure
Including hepatic, renal, cardiac, and pulmonary failure; little evidence-based practice and transfusion strategies vary widely
Other indications
Recurrent splenic sequestration, complicated pregnancy
Controversial indications
Frequent acute pain, chronic pain, avascular joint necrosis, leg ulcers, priapism

3.2 SICKLE CELL TRAIT

In the United States, the prevalence of SCT among African Americans is about 8%, or 1 in 12 African Americans.^{3,9,65,66,67} Sickle cell trait, or sickle cell carriers, are characterized by the presence of both Hb A and Hb S, giving them the genotype Hb AS.^{4,68} The amount of Hb S present can vary among individuals with sickle cell trait. The amount tends to be less than 50%,⁴ with the majority of the red cells containing between 20-45% Hb S.⁴ As previously mentioned, when oxygen levels are decreased, polymerization of Hb S can occur, leading to a sickling process.^{4,68} The amount of sickling that occurs in individuals with sickle cell trait depends on a number of factors, including the amount of Hb S present, along with the degree of hypoxia and other factors that attribute to a sickling event.⁴

3.2.1 Health Implications

Individuals with sickle cell trait are believed to have a benign condition⁴ and are generally asymptomatic with a normal life span.⁶⁹ Studies have demonstrated that individuals with sickle cell trait may actually be at a slightly increased risk for developing sickle hemoglobin-related pathology.^{4,65,69} The potential complications that are associated with sickle cell trait include renal disease,⁷⁰⁻⁷³ thrombosis,⁷⁴⁻⁷⁶ rhabdomyolysis, and the risk for sudden death associated with exercise.^{77,78}

In individuals with sickle cell trait, episodes of hematuria can be common, along with impaired urinary concentrating ability.^{70,71} Urinary infections can be seen in individuals with

sickle cell trait, more frequently occurring in women with sickle cell trait.⁴ The occurrence of these events is closely related to the concentration of Hb S present.^{72,73} Urinary tract infections or sepsis may be a symptom seen in individuals with papillary necrosis, which is the most frequent cause of gross hematuria in individuals with sickle cell trait.⁷⁴

Cases of splenic infarction have occurred at high altitudes in individuals with sickle cell trait.^{4,75,80} Splenic infarction may present as severe abdominal pain, localized to the left upper quadrant.⁸⁰ The spleen may feel tender and enlarged, and individuals may experience nausea and vomiting.⁸⁰

Rhabdomyolysis has been reported in individuals with sickle cell trait, particularly following extreme exertion.⁴ It is believed that extreme physical exertion can lead to damage of the muscle cells (Harrelson). Once muscle cells become damaged, myoglobin and other enzymes are released into the blood. Once myoglobin reaches a certain level in the blood, it is released into the urine, darkening its color, which is known as myoglobinuria. This can then progress to renal failure.⁸¹ Rhabdomyolysis is also defined by increased plasma creatinine kinase (CK) levels, which may be more than five times normal levels.⁸²

Due to these findings, it has been demonstrated that prolonged physical and extreme exertion has been the most significant trigger for serious risks associated with sickle cell trait.^{4,67,80}

3.2.2 Sickle Cell Trait and Exercise

There has been increasing awareness regarding the association of sickle cell trait and sudden death during exercise. It is believed that during periods of extreme physical activity, athletes with sickle cell trait have an increased risk for sudden death, although it is quite rare. It is

hypothesized that if an athlete has sickle cell trait, intense exercise can produce physiological changes to Hb S, leading to polymerization of Hb S,⁸⁰ which in turn creates a sickling event; an event referred to as exertional sickling. Over a ten year period, of 136 sudden, non-traumatic sports deaths in high school and college athletes, seven (5%) were thought to be due to exertional sickling.

The major concerns surrounding an athlete with sickle cell trait include splenic infarction, gross hematuria, and grave exertional rhabdomyolysis.⁶⁵ Given these complications, the most important potential complication of sickle cell trait with exercise is unexpected death.⁸⁰

3.2.2.1 Military

The military first tied sickle cell trait to sudden death during recruit basic training.⁶⁵ The first cases identifying an association between sickle cell trait and sudden death involved four U.S. Army recruits at Fort Bliss, TX.⁶⁷ These four recruits died during or immediately after strenuous exercise during basic training between March of 1968 and February of 1969.⁶⁷ Based on autopsy, it was concluded that the recruits died of diffuse microvascular obstruction from sickled erythrocytes, or “sickle crisis.”⁶⁷ These cases at Fort Bliss demonstrated a strong association of sudden unexplained death with sickle cell trait.⁸⁰

One of the largest military studies was performed by Kark, between January 1, 1977 and December 31, 1981.⁸³ This study enlisted 2.1 million recruits, aged 17-34 years old, who entered basic training during the length of the study.⁸³ Military service records were used to determine which deaths had occurred among recruits during basic training and autopsy files, along with other documentation, was utilized to record the deaths.⁸³ Between 1977 and 1981, 80 deaths occurred, of which, 62 were considered natural deaths occurring during military basic training;⁸³ 35 of the sudden deaths were closely associated with exercise; 13 of these recruits were reported

to have hemoglobin AS, all were African American, and all had sudden deaths related to exercise.

The majority of this data suggests an association between sickle cell trait and exercise-induced sudden death; however, many experts question the validity due to the difficulty of differentiating between postmortem and antemortem sickling. Autopsy reports performed on the recruits indicated the presence of sickled cells in tissues,⁸⁰ although, postmortem sickling is well documented in sickle cell trait and can be expected with death from any cause.⁶⁷ Even though a causal relationship is plausible given the cases of sudden death among recruits, no direct evidence links these deaths to microvascular obstruction by rigid erythrocytes.^{67,80}

3.2.2.2 Athletes

In addition to cases present in military setting there have been a number of cases involving sudden death among athletes, which have been associated with sickle cell trait. A report by Van Camp et al in 1995 illustrated non-traumatic sports-related deaths of high school and college athletes over a ten-year period.⁸⁴ During the duration of this study, 7 deaths with exertional rhabdomyolysis, associated with sickle cell trait, were reported.⁸⁴

3.2.2.3 Guidelines

Although the majority of fatalities associated with sickle cell trait occurred without any knowledge of preceding exercise-related illness, if any warning events occur, they should be taken seriously.⁸⁰ Individuals with sickle cell trait may present with high levels of CK following exercise, exhibit recurring episodes of heat exhaustion, or a serious episode of rhabdomyolysis.⁸⁰ Following the occurrence of any of these warning events, it is suggested that an individual refrain from demanding conditioning or competitive sports, as a precaution.⁸⁰

The major cause of mortality associated with sickle cell trait and exercise appears to be exertional heat illness.⁸⁰ Therefore, a number of precautions are recommended, in an attempt to avoid exertional heat illness. A major contributor to exertional heat illness is dehydration. Adequate hydration is essential at all times surround exercise. This includes staying hydrated before, during, and after exercise.⁸⁰ Adequate hydration may be more difficult, particularly for individuals with sickle cell trait due to a limited capacity for them to concentrate urine, leading to a decreased ability to compensate for negative water balance during exercise.⁸⁰

A sickling event is more often confused with heat cramping, heat exhaustion, or heat stroke.⁸⁵ The most telling symptom of a sickling event is increasing pain and weakness in the working muscles, especially the legs, buttocks, and/or lower back.⁸⁵ Notable differences between heat cramping and a sickling event can be found in Table 4.⁸⁵

Table 4: Notable Differences Between Heat Cramping and Sickling Event⁸⁵

- Heat cramping often has a prodrome. Hours or minutes before the athlete suffers heat cramping, he may see or feel twitching or twinges in tired muscles, those destined to cramp. The athlete who knows heat cramps will tell you, “They are about to come on.” In contrast, sickling has no prodrome.
- The pain is different. Heat-cramping pain is an excruciating pain of sustained, full contraction of muscles, a “lock-up.” Sickling pain is milder, neither the unbearable pain of a heat-cramp lock-up nor the “burning” pain in the thighs as at the end of a middle-distance race. Sickling pain is an ischemic pain from trying to use muscles robbed of blood supply – it is like the pain of intermittent claudication when leg arteries are narrowed by atherosclerosis.
- What stops the athlete is different. With heat cramping, athletes “hobble to a halt” – the fully contracted muscles no longer work. With sickling, athletes “slump to a stop” – the legs become “weak and wobbly” and no longer hold them up.
- The physical findings are different. In major heat cramping, one can see and feel large, rock-hard muscles in full contraction, and the athlete often is writhing and yelling in pain. With sickling, the exhausted player lies fairly still and complains little, except to say that he feels bad and his legs hurt and are weak. The muscles look and feel normal.
- The response is different. After 10-15 minutes sitting in a cold tub, drinking fluids, and getting supplemental oxygen by facemask, the athlete with mild sickling “feels fine.” This is likely because many sickle cells have reverted to normal as they regained oxygen. In contrast, major heat cramping often takes an hour or two to resolve, even in a player resting in the training room, being treated with stretching, massage, and intravenous fluids.

Individuals participating in conditioning activities should allow for gradual buildup. They should begin at an easily tolerated level and work up to near their maximal effort.⁸⁰ If an individual feels ill or is experiencing distressing symptoms, they should limit the amount of exercise they participate in.⁸⁰ This is true, particularly for the two weeks following any viral syndrome, respiratory infection, chest symptoms or syncope.⁸⁰ If an individual is participating in any activities occurring in hot weather conditions, the appropriate adjustment should follow for clothing, work-rest cycles, sun exposure, and an individuals maximum effort put forth.⁸⁰

These precautions may help minimize the risk of severe exertional heat illness; unfortunately, they cannot eliminate the risk of unexpected deaths.⁸⁰ Even though individuals with sickle cell trait may be at a slightly increased risk for these events to occur, these guidelines are important measures that should be followed by everyone who engages in demanding exercise.⁸⁰

The NCAA has also issued precautions for their athletes with sickle cell trait to follow, which are illustrated in Table 5.⁸⁶ If, after following these precautions, a sickling collapse does occur, it should be treated as an emergency and the proper actions should be taken into consideration (Table 6).⁸⁵

Table 5: NCAA precautions for student athletes with sickle cell trait⁸⁶

- Set their own pace
- Engage in slow and gradual preseason conditioning regimen to be prepared for sports-specific performance testing and the rigors of competitive intercollegiate athletes
- Build up their intensity slowly while training
- Use adequate rest and recovery between repetitions, especially during “gassers” and intense station or “mat” drills
- Not be urged to perform all-out exertion of any kind beyond two to three minutes without a breather
- Be excused from performance tests such as serial sprints or timed mile runs, especially if these are not normal sport activities
- Stop activity immediately upon struggling or experiencing symptoms such as muscle pain, abnormal weakness, undue fatigue or breathlessness
- Stay well hydrated at all times, especially in hot and humid conditions
- Maintain proper asthma management
- Refrain from extreme exercise during acute illness, if feeling ill, or while experiencing a fever
- Access supplemental oxygen at altitude as needed
- Seek prompt medical care when experiencing unusual distress

Table 6: Treating sickling collapse as a Medical Emergency⁸⁵

- Check vital signs
- Give supplemental oxygen by face mask
- Cool the athlete, if necessary
- Failing immediate improvement, call 911, attach an AED, and start an intravenous line
- Get the athlete to the hospital quickly
- Tell the doctors to expect explosive rhabdomyolysis and its grave metabolic complications

3.3 SICKLE CELL TRAIT TESTING

3.3.1 Methods

The diagnosis of sickle cell disorders is a fairly simple process. The diagnosis process can be divided into three main categories: tests for sickle hemoglobin, methods for identifying genotype, and methods for distinguishing sub-groups of the genotypes.⁴

Two tests exist that are used to detect sickle hemoglobin. The sickle test was the first test developed to detect sickle hemoglobin, through the process of identifying morphological changes in the red blood cells once they become deoxygenated.⁴ The method created by Daland and Castle (1948) is the standard technique used today, in which a drop of 2% solution of sodium metabisulphite is mixed with one drop of blood on a microscope slide. The sample is then covered with a coverslip and sealed, in order to prevent oxygen from reaching the sample. If sickle hemoglobin is present, sickling usually occurs within one hour and can be visible under a microscope.^{4,87}

The second test, solubility test, is a slightly newer method. Goldberg (1958) utilized the knowledge of the relatively insolubility of deoxygenated sickle hemoglobin in solutions of high molarity to create this method.^{4,88} When combined with buffers, lysing, and reducing agents, samples containing sickle hemoglobin become cloudy, while samples lacking sickle hemoglobin remain clear.⁸⁸ Both tests available for sickle hemoglobin provide information on the presence or absence of sickle hemoglobin; however, these results do not distinguish between different genotypes that account for sickle cell disorders.

In order to differentiate between the genotypes of sickle cell disorders, hemoglobin electrophoresis is the technique utilized.⁴ Hemoglobin electrophoresis is the major technique

used for the diagnosis of sickle cell disorders in the neonatal and postnatal periods of life.⁴ Hemoglobin electrophoresis at alkaline pH is a method commonly used, since some variant hemoglobins have different charges from Hb A at this particular pH.¹ Hb S migrates more slowly towards the anode than does Hb A, while Hb C migrates slower than Hb S.¹ A limitation of this method is the difficulty to differentiate between abnormal hemoglobins of the same charge.⁴ In order to distinguish between these abnormal hemoglobins, DNA analysis would need to be performed.

3.3.2 Military

Prior to 1982, individuals with sickle cell trait were restricted in certain areas of the United States military. These restrictions refrained individuals with sickle cell trait from entering into flight training, aircrew duties, and the U.S. Air Force Academy.⁸⁹ At this time, sickle crises were believed to be the cause of the rare occurrence of unexpected death among individuals with sickle cell trait. Therefore, individuals with sickle cell trait were restricted from precipitating conditions, such as high altitude.

By 1985, the Secretary of Defense stated:

“all military occupational restrictions on sickle cell trait (SCT) bearers are to be removed effective immediately.... No sickle cell trait bearer will be subjected to any additional screening beyond that required of all candidates for that occupation.”⁸⁹

Since this time, each branch of the U.S. military has developed their own policy regarding screening for sickle cell.⁶⁷ In 1996, the Army ceased screening for the sickle gene.⁶⁷ The Marines currently screen all individuals for the sickle gene; however, the Marines impose no restrictions on individuals with sickle cell trait.⁶⁷ The Air Force screens everyone for the sickle

gene. Individuals who are identified as having sickle cell trait are offered the option to decline service.⁶⁷ The Navy also screens all recruits for the sickle gene, but they distinguish recruits with sickle cell trait from others with a neck tag and a red belt during strenuous exercise drills.⁶⁷

3.3.3 Athletes

Over the years, there has been a number of reported sudden death among athletes, which have been associated with sickle cell trait. In 2006, a 19-year-old freshman attending Rice University died following a football practice. His death was attributed to acute exertional rhabdomyolysis associated with sickle cell trait.⁶⁹ In an attempt to bring attention to the event and in the hope of preventing other deaths, the family of the football player filed a lawsuit against the National Collegiate Athletic Association (NCAA) and Rice University.⁶⁹

In 2007, the National Athletic Trainer's Association and the College of American Pathologists recommended that colleges and universities consider screening athletes for sickle cell carrier status in an effort to save lives.⁶⁹ Following the settlement of the lawsuit against the NCAA and Rice University in 2009, the National Athletic Trainers Association (NATA) and the College of American Pathologists (CAP) recommended that all athletes were aware of their sickle cell trait status.⁹⁰ The recommendation was that if an athlete's sickle cell trait status was unknown, the NCAA recommended that athletic departments confirm sickle cell trait status during the Medical Examination period.⁹⁰

Most recently, on April 13, 2010, the legislative council for Division I of the NCAA approved mandatory testing for sickle cell carrier status (sickle cell trait) for all student athletes participating in Division I sports⁶⁹, which went into effect August 1, 2010. The NCAA 2010-2011 Sports Medicine Handbook states that all student-athletes new to their campus are required

to complete a sickle cell solubility test, show results of a prior test, or sign a written release declining the test.⁹¹

4.0 PROGRAM DESIGN

4.1 COLLABORATION WITH UNIVERSITIES

Following the NCAA recommendation in 2009, the University of Pittsburgh Department of Athletics contacted the Children's Sickle Cell Program at Children's Hospital of Pittsburgh regarding testing its athletes for sickle cell trait. At that time, the Children's Sickle Cell Program offered testing services, along with genetic counseling, to the University of Pittsburgh Athletic Department. Contact was created through the athletic training coordinator to establish the coordination of testing for the student-athletes. Contact with the athletic training coordinator was continued throughout the year, and upon the revised recommendations by the NCAA in April of 2010, a modified plan to offer testing services and genetic counseling was established at that time. Seven dates were established, between June and September 2010, at which time the annual physicals were to take place. Genetic counseling and testing occurred during this time. Three additional dates were eventually arranged, at which time student athletes were brought in for the sole purpose of receiving genetic counseling and testing.

The previous year, the University of Pittsburgh offered testing on a voluntary basis. Following the revised recommendations established in 2010, testing remained voluntary; however, if a student athlete declined testing, they were required to sign a waiver, which was provided by the University of Pittsburgh. Additional changes from the previous year included

adjustments to the payment of the testing. Instead of the University of Pittsburgh covering the cost of testing, the testing was billed through each student athletes' personal insurance plan. If a student athlete did not have insurance, they were defaulted to the insurance provided by the University of Pittsburgh. Our program provided our staff's time at no cost and was able to offer the test at a research price of \$12.50 per test.

In lieu of the revised recommendation mandating testing of all Division I student athletes, our program attempted to extend our services to other Division I Athletic Departments in the Pittsburgh area. Contact was established with Duquesne University Department of Athletics Director of Sports Medicine. A similar plan as that initiated at the University of Pittsburgh was established at Duquesne University. Duquesne University elected to mandate testing for all of their incoming student athletes. They did not provide their student athletes with the option opt out of testing by signing a waiver. Five dates were established, at which the annual physicals were to take place. Genetic counseling and testing occurred during this time.

4.2 EDUCATION OF STAFF

In 2009, following the testing process that was provided, educational material was offered to the coaching, training and athletic staff at the University of Pittsburgh, through a PowerPoint presentation (Appendix D). This presentation provided education regarding sickle cell disease, sickle cell trait, and the NCAA's recommendations regarding sickle cell trait. The staff was also provided with prevention measures they could take to ensure the safety of all athletes.

With the addition of Duquesne University in 2010, our program met with members of the coaching, training, and athletic staff at Duquesne University to provide them with the same

educational material. The presentation given to the staff at Duquesne University was previously created and presented by Amy Aloe.

4.3 DATA COLLECTION

4.3.1 Participant Recruitment

The student athletes included in this project are enrolled in the study at the University of Pittsburgh, IRB #PRO10050224. The principle investigator is Dr. Lakshmanan Krishnamurti.

For this project, student athletes from the University of Pittsburgh and Duquesne University were asked if they would like to participate during their physicals, in which they were being tested for sickle cell trait. Participation involved informed consent and the completion of a questionnaire. The addendum consent form for this project can be found in Appendix A. Participants were informed that their results and comments would remain confidential and all identifiers would be removed. A questionnaire was presented to the participants prior to their counseling for the sickle cell trait testing. Following the counseling session and blood draw, another questionnaire was presented. Their participation was not linked to any of their medical or genetic information to the University of Pittsburgh. There was no compensation for participation; 80 student athletes agreed to participate.

4.3.2 Questionnaires

A questionnaire was developed to obtain useful information from student athletes who were undergoing sickle cell trait genetic counseling and testing. These documents can be found in Appendix B. A pre-counseling questionnaire was presented to the student athletes prior to the genetic counseling session and a post-counseling questionnaire was presented to the student athletes following the genetic counseling session and the blood draw.

The pre-counseling questionnaire was comprised of seven questions. The pre-counseling questionnaire contained questions focusing on basic knowledge of sickle cell disease, sickle cell trait, and some differences between the two. Ethnic backgrounds of the participants were also obtained from this questionnaire.

The post-counseling questionnaire was similar to the pre-counseling questionnaire in that it repeated the basic knowledge questions of sickle cell disease, sickle cell trait, and some differences between the two. In addition, the post-counseling questionnaire included questions regarding the patient's experience with undergoing genetic counseling and genetic testing.

4.3.3 Counseling Education

Every student athlete that was to undergo genetic testing received genetic counseling prior to the blood draw for genetic testing. Material presented to the student athletes can be found in Appendix. Sickle cell disease was first covered in the genetic counseling session. Basic information on sickle cell disease and the effect on the red blood cells was discussed, followed by the inheritance pattern of sickle cell disease. Sickle cell disease versus sickle cell trait was discussed and then the following information was broken down into two categories; information

regarding the impact of sickle cell trait on athletes and then the reproductive implications of an individual having sickle cell trait.

For the impact of sickle cell trait on athletes, the athletes were informed that during periods of extreme physical activity, athletes with sickle cell trait have an increased risk for sudden death, although it is important to remember that this is quite rare. It is believed that if an athlete with sickle cell trait participates in intense exercise, an event referred to as exertional sickling may occur. During this event, rapid muscle break down may occur, which can be fatal.

The athletes were informed that collapse due to exertional sickling typically occurs within the first 30 minutes of a practice. Exertional sickling collapse can often be confused with heat exhaustion collapse, therefore, the athletes were presented with a sheet distinguishing these two events. In order to prevent exertional sickling from occurring, the athletes were also provided with various forms of prevention.

Athletes were counseled on an individual basis or in a group of two athletes. Approximately five to ten minutes were spent on counseling and education with each athlete.

4.3.4 Testing

All samples were collected on site at the University of Pittsburgh or Duquesne University's athletic training facilities, respectively, immediately after the genetic counseling was completed. A registered nurse provided by our program performed phlebotomy services. Standard sterile procedures were performed and 2 mL of blood was collected in a sterile lavender-top EDTA collection vial (BD Vacutainer, 5.4 mg EDTA). Following collection, the samples were transported back to Children's Hospital of Pittsburgh diagnostic laboratories within 2-4 hours of collection.

Under the revised NCAA recommendations, student athletes were unable to practice with their team until their carrier status was known, or a waiver was signed. To accommodate these time restraints, our laboratory offered to run all samples through a Hemoglobinopathy evaluation via electrophoresis, with the sole focus on hemoglobin S. Upon the presence of hemoglobin S, that particular sample would then undergo standard Hemoglobinopathy evaluation via electrophoresis and whole red blood cell count.

4.3.5 Results and Disclosure

In accordance with the time restraints, as previously mentioned, under the NCAA recommendations, the laboratory set up a communication plan with our program to run the samples and report the results within 24 hours of collection. The respective athletic training department was contacted by telephone of any positive result.

All results were then faxed to the respective athletic training department within 72 hours. Student athletes with a positive result were contacted by telephone within 24 hours of collection. Each result was then mailed to the corresponding student athlete with a letter interpreting the results. All results were reported.

5.0 RESULTS

5.1 TESTING

Over the course of the testing process, 122 student athletes between the University of Pittsburgh and Duquesne University elected to have sickle cell trait testing. We had a diverse group of athletes, across a variety of sports, including men's and women's soccer teams, track and field, cross country, and men's and women's basketball teams. The population of student athletes varied in terms of gender and race/ethnicity, with the race/ethnicity documented in the questionnaires.

All results were reported to the student athletes. Of the 122 student athletes tested, one athlete was found to have sickle cell trait. Follow up with this particular athlete was attempted without success. This particular athlete ended up leaving the athletic program at the University of Pittsburgh for personal reasons.

5.2 QUESTIONNAIRES

Among the 122 student athletes tested, 80 participated in the questionnaires. Data regarding the race/ethnicity of the participants was collected from the questionnaires. Among those who participated, 57 (71%) were Caucasian, 16 (20%) were African American, and the remaining

athletes were of mixed or other ethnic backgrounds (Figure 3). The pre-counseling and post-counseling questionnaire contained the same five basic knowledge questions regarding sickle cell disease, sickle cell trait, and the differences between the two. I took these five questions and analyzed the answers each student athlete provided for the pre-counseling questionnaire and then for the post-counseling questionnaire.

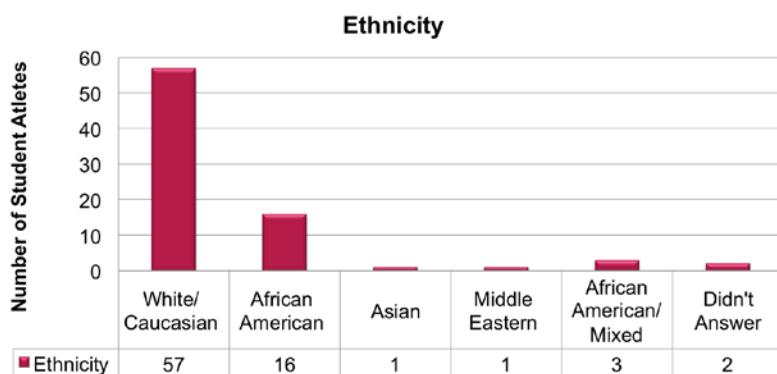


Figure 3: Ethnicity of Student Athletes

For each questions, I first looked to see if the student athlete answered the question correctly on the pre-counseling questionnaire. I continued onto the post-counseling questionnaire, and if they answered the question correctly on the post-counseling questionnaire as well, I considered that as “knowledge known.” If the student athlete did not answer the question correctly on the pre-counseling questionnaire, and when I continued on to the post-counseling questionnaire, they answered the question correctly, I considered that as “knowledge learned.” If there were any other scenarios, such as a student answering the question incorrectly on both the pre- and post-counseling questionnaire, or if they answered the question correctly on the pre-counseling questionnaire but incorrectly on the post-counseling questionnaire, then I considered it “still struggling after counseling.” These steps were then repeated for the four remaining questions. The totals from this analysis can be found in Figure 5.

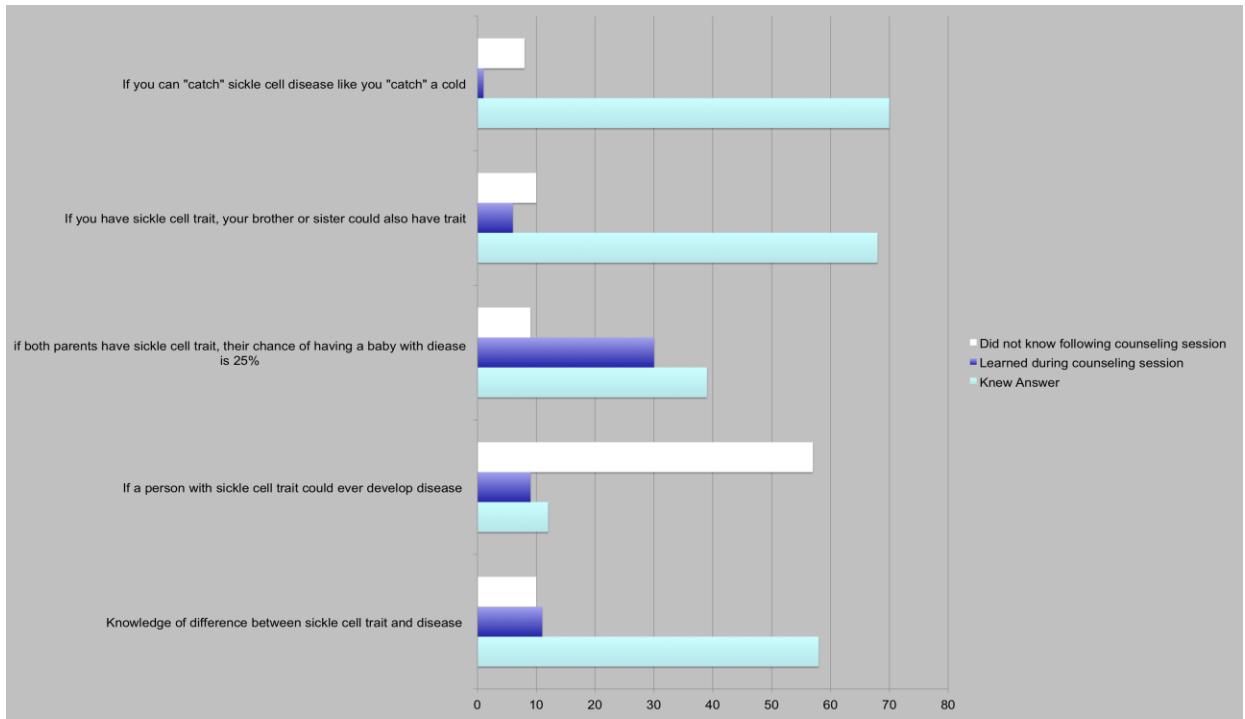


Figure 4: Results from Questionnaires

Once each question was analyzed in such a fashion and the totals calculated, the data from each question was combined, to create a percentage for each level of knowledge: “knew,” “learned,” and “still struggling after counseling;” which is displayed as overall knowledge in Table 7.

Table 7: Overall Knowledge of student athletes gained from the questionnaire

Overall Knowledge	
Knowledge	Percentage of Student Athletes Surveyed
Knew	62%
Learned	14%
Still struggling after counseling	23%

After reviewing these results, a question in particular stood out as seeming confusing for the student athletes. This question asked: “If a person with sickle cell trait could ever develop disease?” Based on the result from that question in particular, 12 student athletes knew the correct answer, 9 student athletes learned the correct answer during the counseling session; however, 57 student athletes seemed to still struggle with this question after counseling. The question was meant to indicate the development of sickle cell disease if an individual has sickle cell trait. It may have been interpreted as developing symptoms associated with an exertional sickling event. Due to the ambiguity of this particular question, it was excluded. Once removed, the new totals were calculated as “Modified Knowledge” (Table 8).

Table 8: Modified Knowledge of student athletes gained from the questionnaires

Modified Knowledge	
Knowledge	Percentage of Student Athletes Surveyed
Knew	74%
Learned	15%
Still struggling after counseling	11%

6.0 DISCUSSION

The NCAA approval of mandatory testing for sickle cell carrier status in April 2010 created an opportunity for our program to extend our services to local Pittsburgh universities. Our program was successful in offering testing services to student athletes at two local Pittsburgh universities: University of Pittsburgh and Duquesne University. Contact was successfully initiated and maintained with the Athlete Departments at these Division 1 universities. During the study, our program complied with the NCAA's ruling to ensure that the athletes and the respective Athletic Departments were aware of the student athletes' carrier status in a timely fashion, prior to their eligibility to practice.

Our program was also effective at providing genetic counseling to the student athletes, prior to their testing for sickle cell trait. The students were provided with educational material regarding sickle cell disease, sickle cell trait, and the potential complications associated with sickle cell trait related to exercise. Guidelines were provided that illustrated preventative measures during times of extreme exercise. Along with this information, the reproductive consequences related to sickle cell disease and sickle cell trait were covered.

The main goal of this study was encased within the third aim of this study. The main objective of this study was to provide the student athletes with questionnaires, one prior to genetic counseling and testing, and one immediately following testing. These questionnaires were collected in an attempt to gain knowledge of the effectiveness of the genetic counseling

prior to sickle cell trait testing. The pre-counseling questionnaire allowed us to gain a better understanding of what the student athletes' knowledge of sickle cell disease and sickle cell trait, prior to any genetic counseling. Based on the data from the pre-counseling questionnaire, the majority of the student athletes had a basic understanding of sickle cell disease and sickle cell trait.

The next step in analysis involved comparing the pre- and post-counseling questionnaires, which allowed us to gain a better understanding of the effectiveness of the genetic counseling that was offered to the student athletes. Based on the analysis of this data, it was clear that one question in particular ("Can a person with sickle cell trait ever develop the disease?"), seemed to confuse the student athletes. The question was meant to ask if an individual with sickle cell trait could ever develop sickle cell disease. It may have been interpreted a different way, such as asking if an individuals with sickle cell trait could ever develop symptoms that are associated with an exertional sickling event. I believe this may be the case due to the fact that a number of student athletes changed their response from "no" to "yes" following the counseling session, at which time we discussed the symptoms associated with an exertional sickling event for individuals with sickle cell trait. Due to this ambiguity of this particular question, future genetic counseling prior to sickle cell trait testing must clarify this information. Emphasis needs to be placed on the difference between sickle cell disease and sickle cell trait, along with the complications that are associated with exercise and sickle cell trait.

Aside from this single question of confusion, there still was not 100% knowledge of sickle cell disease and sickle cell trait. Due to this evidence, genetic counseling is an important part of any genetic testing process. Individuals, particularly student athletes, must be aware of

the testing they are undergoing, along with the impact the information will have on their life. For student athletes, not only does sickle cell trait testing have an impact on their athletic careers, but also on their reproductive futures. Therefore, genetic counseling should be an essential part of the testing process among all student athletes complying with the NCAA ruling.

6.1 FUTURE DIRECTION OF TESTING

Much controversy surrounded the April 13, 2010 NCAA ruling mandating sickle cell trait testing for all Division I student athletes. In previous years, sickle cell trait testing for student athletes was simply recommended, left up to the discretion of individual programs. Once mandated, many disputed the ruling, stating that it took away student athletes' right to decide for themselves whether they wanted to undergo genetic testing or not.

A similar event occurred at the University of California, Berkeley during the summer of 2010. The University of California, Berkeley decided to offer the freshman the opportunity to screen for three specific genes and called the project "Bring Your Genes to Cal".⁹² Variants of these genes would provide the students with more information on their ability to absorb folic acid, their ability to tolerate alcohol, and their ability to metabolize lactose.⁹³ All freshman were sent a DNA saliva kits and asked to turn them on a voluntary basis. This program gained rapidly gained media attention and state health officials did end up ruling that this program violated state law due to the release of the test results to the students who volunteered their DNA.⁹² The controversy surrounding this program may set a bad precedent for the future direction of genetic testing.⁹²

Other controversies surrounding the NCAA ruling included the concern for isolation of individuals at risk for being sickle cell trait carriers, along with those who tested positive for having sickle cell trait. With the limited contact made between our program and the Athletic training staff at the University of Pittsburgh, some discussion occurred involving the treatment of student athletes with sickle cell trait. Athletic trainers expressed their feelings that student athletes with sickle cell trait would not be treated any differently. The mission of athletic trainers is to be aware of each individual student athletes' abilities and limitations and to keep in mind what is best for each student athlete.

A limitation of our study is that we did not have contact with any student athlete with sickle cell trait at the University of Pittsburgh or Duquesne University. Having contact with a student athlete with sickle cell trait may have provided more insight on the impact the results had on those particular student athletes' life and athletic career.

Future plans include enrolling the Athletic Department Staff at the University of Pittsburgh in a questionnaire including questions surrounding the potential impact a positive result may have on a student athlete, particularly dealing with how a student athlete may be treated by the staff, along with the impact it may have on an athletes future on the field and off. Additional future plans include more education for student athletes regarding the testing process. A fear in the public is that student athletes may not have a solid understanding of the intention of the testing process; they may feel pressured into taking the test or pressured into not taking the test. Due to the public's fear that the testing may isolate a student athlete or lead to discrimination of student athletes with sickle cell trait, the student athletes themselves may also fear that and decide to opt out of testing. Individuals with sickle cell trait may then go undetected and a sickling event may occur without warning, which may sadly lead to sudden

death in athletes. Testing student athletes for sickle cell trait allow the athletic training and coaching staff to be aware of health concerns for those individuals, allowing for greater awareness of the warning signs of a sickling event.

In conclusion, continuing this program, with the possibility of expanding to additional athletic programs, allows for better awareness and understanding of sickle cell trait and the impact on athletes. Genetic counseling needs to play a larger role in various athletic programs across the country, which are offering sickle cell trait testing to their athletes. The combination of the education and genetic counseling will ensure student athletes and the athletic staff have a solid understanding of sickle cell trait and impact on exercise.

APPENDIX A

INSTITUTIONAL REVIEW BOARD CONSENT FORM

CONSENT TO ACT AS A PARTICIPANT IN A RESEARCH STUDY

Title: Sickle Cell Trait Counseling for Student-Athletes

PRINCIPAL INVESTIGATOR:

Lakshmanan Krishnamurti, M.D.
Director, Comprehensive Hemoglobinopathy Program
Division of Pediatric Hematology/Oncology
Children's Hospital of Pgh, Floor 9
Telephone: 412-692-7192

CO-INVESTIGATORS:

Victoria Costanzo, B.S.
Genetic Counseling M.S. Student
University of Pittsburgh
Graduate School of Public Health
Department of Genetics
Telephone: 412-692-7827

The purpose of this research study is to evaluate the genetic counseling that is provided prior to the Sickle Cell Trait testing offered. For that reason, we will be surveying student-athletes and ask them to complete a brief (approximately 10 minute) survey. A survey will be provided prior to the genetic counseling along with immediately following the genetic counseling. A follow-up phone call will take place a week following the counseling. There will be no costs for participating in this study. In addition, you understand that you will not receive payment.

If you are willing to participate, our survey will ask about your background (e.g., race), as well as your feelings about the counseling and testing that is being offered to you. There are no direct benefits to you if you decide to participate in this study. The risks of participating are minimal. This includes breach of confidentiality. To minimize this risk, your name will be removed from the surveys and replaced with a code. The record that contains the identifiers to these codes will be kept in a secure location and will only be accessible to personnel involved in the study.

In addition to the investigators listed on the first page of this authorization (consent) form and their research staff, the following individuals will or may have access to identifiable information (which may include your identifiable medical information) related to your participation in this research study:

Authorized representatives of the University of Pittsburgh Research Conduct and Compliance Office may review your identifiable research information (which may include your identifiable medical information) for the purpose of monitoring the appropriate conduct of this research study.

In unusual cases, the investigators may be required to release identifiable information (which may include your identifiable medical information) related to your participation in this research study in response to an order from a court of law. If the investigators learn that you or someone with whom you are involved is in serious danger or potential harm, they will need to inform, as required by Pennsylvania law, the appropriate agencies.

All responses to the surveys will be confidential and results will be kept under lock and key. Your participation is voluntary, and you may withdraw from this project at any time. Your decision to withdraw or



not participate in this research study will have no effect on your current or future relationship with the University of Pittsburgh. Any information provided prior to a withdrawal may continue to be used for the purposes described above.

VOLUNTARY CONSENT

The above information has been explained to me and all of my current questions have been answered. I understand that I may contact the Human Subjects Protection Advocate of the IRB Office, University of Pittsburgh (1-866-212-2668) to discuss problems, concerns, and questions; obtain information; offer input; or discuss situations that have occurred during my participation.

By signing this form, I agree to participate in this research study. A copy of this consent form will be given to me.

Participant's Signature

Printed Name of Participant

Date

CERTIFICATION of INFORMED CONSENT

I certify that I have explained the nature and purpose of this research study to the above-named individual(s), and I have discussed the potential benefits and possible risks of study participation. Any questions the individual(s) have about this study have been answered, and we will always be available to address future questions as they arise."

Printed Name of Person Obtaining Consent

Role in Research Study

Signature of Person Obtaining Consent

Date

APPENDIX B

QUESTIONNAIRE

B.1 PRE-COUNSELING QUESTIONNAIRE

Survey for Student Athletes
Sickle Cell Trait testing pre-counseling

Today you will see a Genetic Counseling student to discuss Sickle Cell trait testing that is required by the NCAA for all prospective Division I Athletes. You agree to be a part of a research study by filling out this survey. All answers will be confidential and you can refuse to answer any questions.

Have you heard about sickle cell disease or sickle cell trait before today?

YES NO

Is there a difference between sickle cell trait and sickle cell disease?

YES NO

Can a person with sickle cell trait ever develop the disease?

YES NO

If both parents have sickle cell trait, is their chance of having a baby with disease 25%?

YES NO

If you have sickle cell trait, can your brother or sister also have the trait?

YES NO

Can you “catch” sickle cell disease like you “catch” a cold?

YES NO

Which of the following best describes your ethnic background?

- African American
- American Indian or Eskimo
- Asian or Pacific Islander
- Latino/Hispanic
- White/Caucasian
- Some other ethnic background

Please explain: _____

Prefer not to answer

B.2 POST-COUNSELING QUESTIONNAIRE

Survey for Student Athletes # _____
Sickle Cell Trait testing follow-up

Today you were seen by a Genetic Counseling student to discuss Sickle Cell trait testing that was required by the NCAA for all prospective Division I Athletes. You agree to be a part of a research study by filling out this survey. All answers will be confidential and you can refuse to answer any questions.

Have you heard about sickle cell disease or sickle cell trait before your physical?

YES NO

Was it clear that there is a difference between sickle cell trait and sickle cell disease?

YES NO

Can a person with sickle cell trait ever develop the disease?

YES NO

If both parents have sickle cell trait, is their chance of having a baby with disease 25%?

YES NO

If you have sickle cell trait, can your brother or sister also have the trait?

YES NO

Can you “catch” sickle cell disease like you “catch” a cold?

YES NO

Did you feel anxious before meeting with the genetic counselor today?

Rating: 0 (not anxious) 1 (somewhat worried) 2(very anxious/concerned)

Did the genetic counselor answer your questions to your satisfaction?

YES NO

Any additional comments? _____

Did you have blood drawn for the testing at your physical?

YES NO

Did you tell siblings or other family members you were getting testing done today?

YES NO

Was anyone upset that you were having testing done?

YES NO

Please explain: _____

APPENDIX C

EDUCATIONAL MATERIALS PROVIDED TO STUDENT ATHLETES

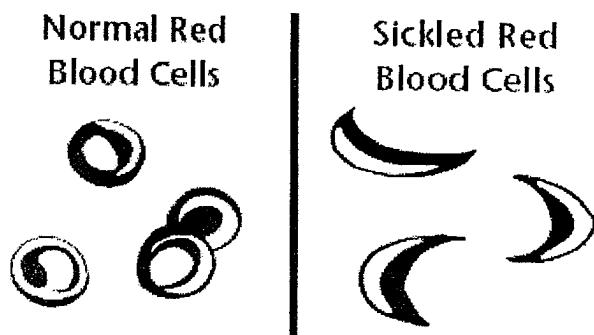
Sickle Cell Trait and YOU, the Athlete

There has been increasing awareness regarding sickle cell trait and sudden death during exercise. *This occurrence is very rare and can be completely avoided by following a few simple guidelines.* This handout is intended to answer any questions you have about being an athlete with sickle cell trait. First, we need to explain the difference between sickle cell disease and trait.

Sickle Cell Disease vs Sickle Cell Trait

Sickle cell disease is a serious blood disorder, in which a genetic change causes the red blood cells to change shape from round and soft to half-moon shaped and hard.

Sickled cells can group together and block blood vessels, causing harmful complications in the body. Individuals with sickle cell disease inherit one copy of the sickle cell gene from each of their parents.



Sickle cell trait is not a disease, and will never turn into a disease. Individuals with sickle cell trait have one copy of the gene for sickle cell and one copy of the gene for healthy red blood cells. Sickle cell trait is found in 8% of African-Americans. It is also common in people of African, Mediterranean, Middle Eastern and Indian origin.

Exercise and the Athlete with Sickle Cell Trait

During periods of extreme physical activity, athletes with sickle cell trait have an increased risk for sudden death, although it is important to remember that this is quite rare. While this association exists, there is no direct evidence as to why. It is hypothesized that if an athlete has sickle cell trait, intense exercise can cause changes in the body known to cause sickling. This occurrence is called exertional sickling. Over a ten year period, of 136 sudden, non-traumatic sports deaths in high school and college athletes, seven (5%) were thought to be due to exertional sickling.

Exertional Sickling Collapse

Exertional sickling can lead to rapid muscle break down, called rhabdomyolysis, which can be fatal. If an athlete collapses from exertional sickling, it may be mistaken for heat or cardiac collapse. In cardiac collapse, the collapse is "instantaneous," without any cramping and the athlete unable to talk. Exertional sickling collapse typically occurs within the first 30 minutes of practice, with less pain than heat exhaustion collapse and no muscle twinges. While in heat exhaustion collapse the muscles lock up and feel hot to the touch, in an exertional sickling collapse the muscles feel weak, but normal to the touch.

Type	Muscle Twinges	Timing in Activity	Pain	Muscles
Heat	Yes	Later	More	Locked-up and hard to the touch
Sickling	No	Within first 30 minutes	Less	Weak and feel normal to the touch

If an exertional sickling collapse should be treated as an emergency. Call 911 and tell emergency personnel to expect rhabdomyolysis.

New NCAA Recommendations

The National Collegiate Athletic Association (NCAA) recently began recommending that all of its athletes be tested for sickle cell trait. The NCAA also states that athletes with sickle cell trait should not be prevented from participating in competitive sports. One can be tested for sickle cell trait with a simple, inexpensive blood test.

Prevention of Exertional Sickling

Although exertional sickling is a serious condition, it can easily be prevented. It is recommended that athletes with sickle cell trait be allowed to:

- acclimate themselves gradually to strenuous drills
- set their own pace and drink plenty of water
- Precaution should be taken especially at high altitudes, during hot days (greater than 90 degrees), or periods of illness.

If these guidelines are followed, exertional sickling can be avoided.

For more information, please contact us at:

Children's Hospital of Pittsburgh of UPMC Sickle Cell Program

Phone: 412-692-6059

Where should I go with more questions?

Doctors, nurses and genetic counselors at Children's Hospital of Pittsburgh of UPMC are available to answer your questions.

For More Information and Testing

- **Children's Hospital of Pittsburgh of UPMC**
Division of Pediatric Hematology/
Sickle Cell Program
412-692-6059

- **Children's Sickle Cell Foundation Inc.**

www.csckids.org

412-537-8973

Gove Business Center

226 Paul St.

Pittsburgh, PA 15211

- **Magee-Womens Hospital Medical Genetics**

412-641-4168 or

1-800-454-8155

- **Sickle Cell Disease Association of America**

www.sicklecelldisease.org

- **Sickle Cell Society Inc.**

412-371-0628

7643 Frankstown Ave

Pittsburgh, PA 15208



Children's
Hospital of Pittsburgh

of UPMC

www.chp.edu

CSCf | **Children's**
Sickle Cell
Foundation, Inc.

IS IT IN
YOUR GENES?

UNDERSTANDING

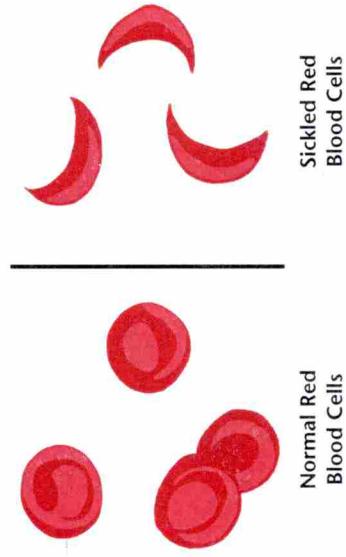
SICKLE CELL
Trait

UNDERSTANDING Sickle Cell Trait

What is sickle cell disease?

SICKLE CELL DISEASE is a serious disease of the red blood cells that causes the cells to change their shape.

It can be a very painful disease. Sickle cell disease is caused when each of your parents passes to you a non-working gene, before birth. You cannot catch it from being around someone with sickle cell disease.

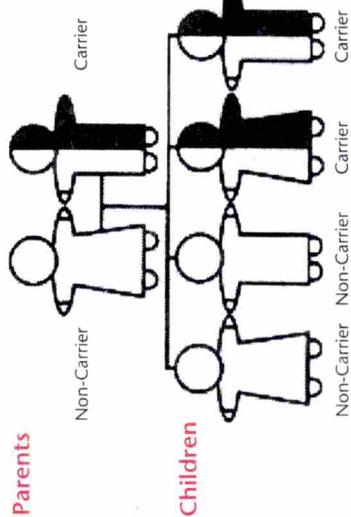


What is sickle cell trait?

SICKLE CELL TRAIT occurs when a person inherits a working gene (A) and a nonworking sickle gene (S). People with sickle cell trait are also called “carriers”. Sickle cell trait is not a disease. People with sickle cell trait cannot tell they have it without being tested. If two people who have sickle cell trait have a baby, that child is at risk to receive a nonworking sickle (S) gene from each parent, which will cause sickle cell disease.

The most important reason to be aware of sickle cell trait is to find out if you can possibly have a baby with sickle cell disease. The only way to find out is for you and your partner to get tested. The different genes for the disease come from both parents — not just one.

When one parent is a carrier



What can I do if I have sickle cell trait?

If you find out that you have sickle cell trait, your spouse or partner should also be tested. Knowing ahead of time that your future children may be at risk gives you time to prepare for and learn more about caring for a child with a serious illness. Genetic counselors are also available to help explain the risks and discuss prenatal testing, and other options. The most important thing you can do is be responsible for the best health care for your child.

Who is at risk for sickle cell trait?

Anyone can carry a sickle cell trait; however, some populations are at a higher risk than others are. Sickle cell trait is most common in African Americans. However, people of Mediterranean, Middle Eastern, Indian, Asian and Hispanic backgrounds are also at an increased risk to have sickle cell trait so many people should be tested.

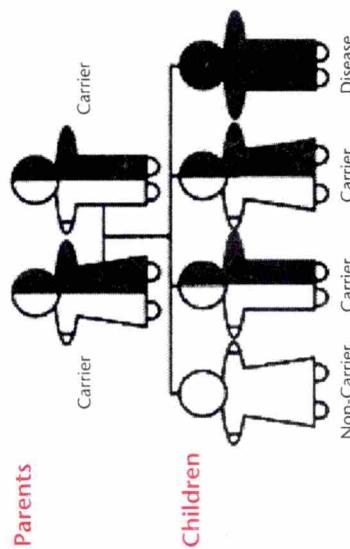
How can you tell if someone has sickle cell trait?

The only way to tell of someone has sickle cell trait is to be tested. Some blood tests are more useful than others. The best tests give detailed results. They can find the (S) gene. But they can also find other genes, such as the (C) gene or the Beta thalassemia gene, which can combine with the (S) gene to cause other forms of sickle cell disease.

What can I do if I have sickle cell trait?

If you find out that you have sickle cell trait, your spouse or partner should also be tested. Knowing ahead of time that your future children may be at risk gives you time to prepare for and learn more about caring for a child with a serious illness. Genetic counselors are also available to help explain the risks and discuss prenatal testing, and other options. The most important thing you can do is be responsible for the best health care for your child.

When both parents are carriers



What is a gene?

Genes are the instructions that parents pass to their children for different traits such as eye color or diseases such as diabetes. We have two copies of every gene in our body. We receive one copy from our mother and one from our father before birth. There is no way to control which genes are passed from parents to children. The sickle gene (S) affects the red blood cells.

APPENDIX D

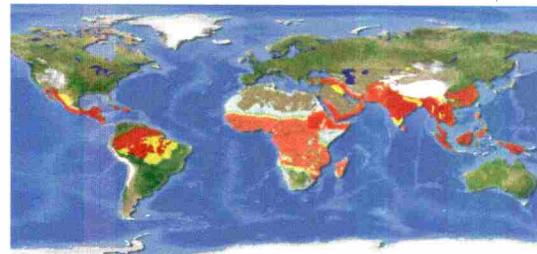
**PRESENTATION GIVEN TO THE ATHLETIC ADMINISTRATORS, TRAINERS, AND
COACHES AT THE UNIVERSITIES**

Sickle Cell Trait and the Athlete

Lakshmanan Krishnamurti, MD
Amy Aloe, BA



Prevalence



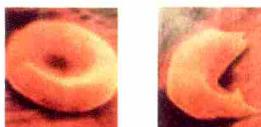
- Those of African, Mediterranean, Middle Eastern, Caribbean, South American and Central American decent are at risk for sickle cell disease

Prevalence of Sickle Cell Disease and Trait



- Sickle Cell Disease
 - 1 in 375 (0.26%) African Americans are born with sickle cell disease
- Sickle Cell Trait
 - 8% of African Americans are carriers
 - 0.046% of nonblack Americans are carriers

What is sickle cell disease?

- A serious blood disorder, in which a genetic change causes the red blood cells to change shape from round and soft to half-moon shaped
- 
- a person needs to inherit a copy of the nonworking gene from both parents to have disease

Normal vs Sickle Hemoglobin



Normal	Sickle
• disc-Shaped	• sickle-Shaped
• soft (like a bag of jelly)	• hard (like a piece of wood)
• easily flow through small blood vessels	• often get stuck in small blood vessels
• lives for 120 days	• lives for 20 days or less



Sickle Cell Disease

- Sickle cells can block blood vessels, which cause serious complications such as
 - Hand Foot Syndrome
 - Painful swelling for hands and feet caused by sickled red blood cells
 - One of the first manifestations, occurring most often between 6mo-2yrs
- 

Sickle Cell Disease



- Sickle cells can block blood vessels, which cause serious complications such as
 - Acute Chest syndrome
 - Caused by sickled cells blocking blood vessels in the lungs
 - Most common cause of childhood death in sickle cell disease



Sickle Cell Disease



- Sickle cells can block blood vessels, which cause serious complications such as
 - Hand Foot Syndrome
 - Acute Chest syndrome
 - Anemia
 - Low number of red blood cells

Sickle Cell Disease



- Sickle cells can block blood vessels, which cause serious complications such as
 - Hand Foot Syndrome
 - Acute Chest syndrome
 - Anemia
 - Jaundice
 - Increased levels of liver enzyme in the blood, due to break down of red blood cells

Sickle Cell Disease



- Sickle cells can block blood vessels, which cause serious complications such as
 - Hand Foot Syndrome
 - Acute Chest syndrome
 - Anemia
 - Jaundice
 - Infection

Sickle Cell Disease



- Sickle cells can block blood vessels, which cause serious complications such as
 - Hand Foot Syndrome
 - Acute Chest syndrome
 - Anemia
 - Jaundice
 - Infection
 - Eye problems

Sickle Cell Disease



- Sickle cells can block blood vessels, which cause serious complications such as
 - Hand Foot Syndrome
 - Acute Chest syndrome
 - Anemia
 - Jaundice
 - Infection
 - Eye problems
 - Stroke

Sickle Cell Disease

- Sickle cells can block blood vessels, which cause serious complications such as
 - Hand Foot Syndrome
 - Acute Chest syndrome
 - Anemia
 - Jaundice
 - Infection
 - Eye problems
 - Stroke
 - Splenic sequestration
 - Sudden pooling of blood in the spleen

Sickle Cell Disease

- Sickle cells can block blood vessels, which cause serious complications such as
 - Hand Foot Syndrome
 - Acute Chest syndrome
 - Anemia
 - Jaundice
 - Infection
 - Eye problems
 - Stroke
 - Splenic sequestration
 - Sickle cell pain crisis

National Sickle Cell Anemia Control Act

- Signed by president Nixon in 1972
- Allocated funds to provide for:
 - voluntary sickle cell trait screening and counseling
 - Sickle cell education for health professionals and the public
 - Research and research training for diagnosis, treatment, and control of sickle cell disease

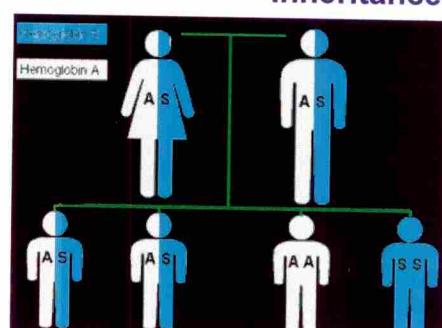
National Sickle Cell Anemia Control Act

- As a result, the outcome for an individual with sickle cell disease is dramatically different
 - Mortality rate dropped 41-52% between 1968 and 1992
 - In 1960, the disease was primarily one of childhood with limited survival to adulthood
 - Now average lifespan for males with sickle cell disease is 42 and for females with sickle cell disease is 48

What is sickle cell trait?

- Sickle cell trait occurs when a person inherits a working gene from one parent and a nonworking (sickle) gene from the other parent
- Also referred to as being a “carrier”
- Sickle cell trait is not a disease

Autosomal Recessive Inheritance



National Collegiate Athletic Association (NCAA) Recommendation

- On June 25th, the NCAA's Committee on Competitive Safeguards and Medical Aspects of Sports recommended that its member colleges and universities test athletes for Sickle Cell Trait during their required medical examinations, if not already known
- Follows guidelines from the National Athletic Trainers Association and the College of American Pathologists and stems from a recent lawsuit resolution

National Collegiate Athletic Association (NCAA) Recommendation

- The lawsuit was filed against the NCAA by the family of Dale Lloyd II
 - a former football student-athlete at Rice University, who died in 2006 after a practice
 - After his untimely death, testing indicated he was a sickle cell trait carrier and that this had lead to his death

History of Sickle Cell Trait and Death in Athletes & the Military

- In the past 7 years, sickling has been correlated to the death of at least 9 athletes
 - 5 college football players in training
 - 2 high school athletes
 - 2 middle school athletes
- In the U.S. military, sickle cell trait was tied to sudden death during recruit basic training
 - They found that recruits with trait were 30 times more likely to die during basic training, than recruits without sickle cell trait

History of Sickle Cell Trait and Death in Athletes & the Military

- Of the sudden deaths
 - In the athletes
 - Often occurred early in the season, usually after sprinting 800-1600 meters
 - In the army
 - Most occurred during the 1st month of training and associated with exertional activities requiring maximum effort

Debate over cause of sudden death

- There is no direct evidence linking the pathogenesis of exercise-related sickling; however the majority of data shows that sickle cell trait is associated with increased risk of exercise-induced sudden death

Evidence supporting sickling during exercise

- Strenuous exercise may cause sickling, as it causes four changes in the body that foster sickling
 - Severe hypoxemia (low oxygen)
 - Metabolic acidosis
 - Muscle hyperthermia
 - Red-cell dehydration

Evidence supporting sickling during exercise

- Strenuous exercise may cause sickling, as it causes four changes in the body that foster sickling
 - Severe hypoxemia (low oxygen)
 - Metabolic acidosis
 - Muscle hyperthermia
 - Red-cell dehydration

↓

To facilitate oxygen delivery

Evidence supporting sickling during exercise

- When there is low oxygen levels in the blood, the sickle hemoglobin has an increased affinity to bind to the healthy red blood cells
- These collections of blood cells can block blood flow to the muscles, causing rapid muscle breakdown, leading the athlete to collapse

Exertional Sickling

- The sickling that occurs during all-out physical activity, is called "exertional sickling"
- The muscle breakdown that it causes, can be fatal
- Heat, dehydration, high-altitudes and asthma can increase the risk and severity of exertional sickling

Features of Collapse Due to Sickling

- When an athlete collapses from exertional sickling, it may be mistaken for heat or cardiac collapse
- In cardiac collapse, the collapse is "instantaneous," without any cramping, and athletes are unable to talk
- Differences between heat and sickling collapse:

Type	Muscle twinges	Timing in activity	Pain	Muscles
Heat	Yes	Later	More	Locked-up and hard to the touch
Sickling	No	Within first 30 minutes	Less	Weak and feel normal to the touch

Sickle Cell Trait in the Military

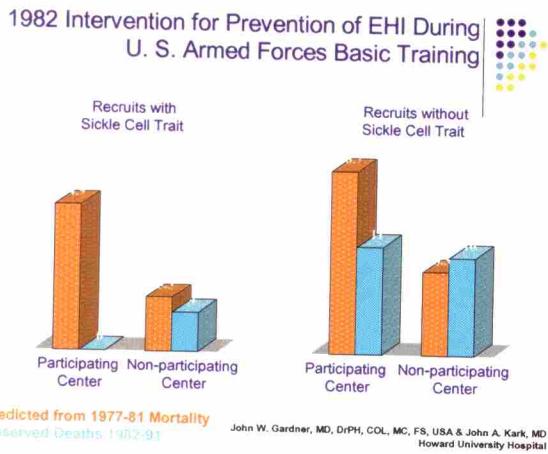
- Army
 - Ceased screening for sickle cell trait
- Marines
 - Screen all participants and do not alter training regimens
- Air Force
 - Screen all participants and offers the option to each recruit to decline service if positive for trait
- Navy
 - Screen all recruits and identifies trait carriers with a red belt and neck tag during strenuous exercise drills

Sickle Cell Trait in the Military

- 1982 Intervention for Prevention of Exertional Heat Illness (EHI) During U. S. Armed Forces Basic Training
- Record wet-bulb globe temperature (WBGT) at least hourly at the exercise site
 - WBGT composite temperature used to estimate the effect of temperature, humidity, wind speed, wind chill, and solar radiation on humans (range from \$50-\$150)
- Decrease exercise intensity and increase rest cycles as WBGT rises, to minimal effort at 90°F
- Increase water intake & observe water consumption
- Exercise using light track clothing in hot weather
- Initiate immediate cooling/rehydration with early symptoms



John W. Gardner, MD, DrPH, COL, MC, FS, USA & John A. Kark, MD
Howard University Hospital



1982 Intervention for Prevention of EHI During U. S. Armed Forces Basic Training Conclusions

- There is a strong association between exposure to hot weather within 24 hours of exercise and risk of exercise-related sudden death, strongest with sickle cell trait.
- Exertional heat stroke greatly increases the risk for exercise-related threatened or actual sudden death, probably through cardiovascular collapse.
- Intervention to prevent exertional heat illness appears to eliminate the excess risk for exercise-related death with sickle cell trait and to reduce mortality in others.
- Exertional heat illness is a major preventable factor contributing to exercise-related death of young adults.

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Testing for Sickle Cell Trait at the University of Pittsburgh

- We tested 79 athletes from the following teams
 - Football
 - Softball
 - Men's and Women's Soccer
 - Swimming
 - Track & Field
 - Cross Country
 - Men's and Women's Basketball
- Offered on-site education at time of testing and provided results over the phone to athletes

National Athletic Trainers' Association Recommendations to Prevent Exertional Sickling

- Build up slowly in training with pace and progressions, allowing longer periods of rest and recovery
- Encourage participation in preseason strength and conditioning programs to enhance the preparedness of athletes for sport-specific performance testing
 - Athletes with sickle cell trait should be excluded from participation in performance tests, such as mile runs, serial sprints, etc.

National Athletic Trainers' Association Recommendations to Prevent Exertional Sickling

- Cessation of activity with onset of symptoms
 - Muscle "cramping"
 - Pain
 - Swelling
 - Weakness
 - Tenderness
 - Inability to "catch breath"
 - fatigue

National Athletic Trainers' Association Recommendations to Prevent Exertional Sickling

- Let athletes set their own pace
- All athletes should participate in year-round, periodized strength and conditioning program consistent with their individual needs, sport, and abilities
- Educate athletes to create an environment in which they feel comfortable reporting any symptoms immediately

National Athletic Trainers' Association Recommendations to Prevent Exertional Sickling

- More extreme conditions, such as hot temperatures, dehydration, asthma, illness, and higher altitudes predispose the athlete with sickle cell trait to exertional sickling. At these times special care should be taken:
 - Adjust work/rest cycles
 - Emphasize hydration
 - Control asthma
 - If ill, an athlete should not practice
 - In increased altitudes, modify training and have supplemental oxygen available

National Athletic Trainers' Association Recommendations to Treat Exertional Sickling Collapse

- Treat as an emergency
 - Check vital signs
 - Administer high-flow oxygen (15 lpm if available) with a non-rebreather face mask
 - If necessary, cool the athlete
 - If vital signs decline, call 911, attach an AED, start an IV and get the athlete to the hospital ASAP
 - Tell doctors to expect explosive rhabdomyolysis (muscle breakdown) and grave metabolic complications
- Prepare for this scenario by having an emergency plan and appropriate equipment for all practices and competitions

Participation of Athletes with Sickle Cell Trait

- Athletes with sickle cell trait should NOT be excluded from participating in sports, as screening and the simple precautions listed previously may prevent exertional sickling

Genetic Information Nondiscriminatory Act (GINA)

- Signed by president George W. Bush in 2008
- Prevents insurance and employment discrimination based on genetic information
- Genetic information includes:
 - Individual genetic test results
 - Genetic tests of family members or fetuses
 - Manifestation of disease or disorder in family members
 - Any request for, or receipt of, genetic services or participation in clinical research that includes genetic services (genetic testing, counseling, or education) by an individual or family member.

Participation of Athletes with Sickle Cell Trait

- Great care should be taken to avoid stigmatization of athletes with sickle cell trait
- If discrimination or stigmatization occurs, it could discourage athletes to be screened for sickle cell trait or take appropriate measures during practice if feeling fatigued
 - This would be to the detriment of the athlete's health and well-being

In closing...

- How can the University of Pittsburgh
 - ensure that it's athletes with sickle cell trait are not discriminated against?
 - foster an environment in which athletes feel comfortable getting tested?
 - run practices to ensure the safety of all athletes? Since testing for sickle cell is voluntary, the trait status of all athletes may not be known.

Thank You



- Thank you to all coaches and administrators for organizing the sickle cell trait screening with your athletes
- Any questions?

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