

## Screening U.S. College Athletes for Their Sickle Cell Disease Carrier Status.

By: Lanetta B. Jordan, Kim Smith-Whitley, Marsha J. Treadwell, Joseph Telfair, Althea M. Grant, and Kwaku Ohene-Frempong

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### **Abstract:**

There are many issues surrounding the screening of collegiate athletes for their sickle cell disease carrier status (or sickle cell trait), a genetic condition. This paper summarizes the establishment of expert advice given to the Secretary's Advisory Committee on Heritable Disorders in Newborns and Children (SACHDNC) on the issue. The SACHDNC has developed a report to advise the Secretary of the USDHHS about the 2010 rule of the National Collegiate Athletic Association (NCAA) requiring testing for sickle cell trait in all incoming Division I student athletes. The SACHDNC does not support the NCAA's rule to screen collegiate athletes for sickle cell trait.

**Keywords:** preventative medicine | sickle cell disease | sickle cell disease testing | sickle cell genetic trait | collegiate athletes | medicine | public health | blood disorders

### **Article:**

#### Introduction

The number of people with sickle cell trait (SCT) in the U.S. is not accurately known; however, extrapolating U.S. newborn screening data (genes-r-us.uthscsa.edu/resources/newborn/00/ch13\_complete.pdf) to the U.S. population (2010.census.gov/2010census/data/) would yield approximately 4 million people, and worldwide, the estimate is more than 300 million people with SCT (also known as hemoglobin [Hb] AS).<sup>1</sup> Sickle cell trait occurs in high frequency among people of African or Middle Eastern descent, but it is also common among those of Indian, or Mediterranean origin.<sup>2</sup> People with SCT are generally healthy carriers of the gene that causes sickle cell disease (SCD). Sickle cell disease is a serious health condition that requires medical treatment. Unlike people with SCD, those with the trait do not require regular medical treatment, and for the overwhelming majority,

SCT does not affect their health. People with SCT can pass the sickle cell gene to their children and, depending on what genes their reproductive partners carry, they can have children with SCD. For this reason, it is advisable for people to know whether they have SCT.

This paper represents the work of a committee of experts set up by the Secretary's Advisory Committee on Heritable Disorders in Newborns and Children (SACHDNC) to develop a briefing paper to assist the SACHDNC on developing its recommendations (<http://www.hrsa.gov/advisorycommittees/mchbadvisory/heritabledisorders/recommendations/correspondence/sicklecell061410.pdf>) for the Secretary of the USDHHS regarding the rule made by the National Collegiate Athletic Association (NCAA) in 2010 requiring all incoming Division I student athletes to be tested for SCT. The SACHDNC advised the Secretary that there was an insufficient scientific and public health basis for the mass screening of athletes for SCT.

An important aspect of the public health approach to screening is the recognition that screening for SCD, SCT, and related hemoglobinopathies, like all genetic testing, should include health education to explain the benefits and risks of testing, and genetic counseling to explain the results and their implications. For nearly 3 decades, screening for SCD and related hemoglobinopathies has been part of state public health newborn screening programs in the U.S. to identify affected children early and to provide preventive medical treatment and health education to their parents in order to prevent early death from infection. Screening of other members of the general public for sickle cell carrier status and other hemoglobin disorders is not mandatory, but voluntary, and is done usually for genetic counseling purposes.

Sickle cell trait is defined by the inheritance of a normal  $\beta$ -globin gene ( $\beta$ A) from one parent and sickle  $\beta$ -globin gene ( $\beta$ S) from the other parent. In SCT, every red blood cell contains both the normal hemoglobin A (Hb A) and the sickle hemoglobin S (Hb S), with Hb A always predominant in quantity. The predominance of Hb A in SCT explains the normal behavior of SCT red cells under most physiologic conditions. Sickle cell trait is different from SCD because in SCD, unlike SCT, both  $\beta$ -globin genes, one from each parent, are abnormal; either both are  $\beta$ S, or one is  $\beta$ S and the other is a gene for another  $\beta$ -globin variant, or a gene for  $\beta$ -thalassemia. In SCD, Hb S is the predominant hemoglobin (beyond the neonatal period) and that accounts for the pathology associated with the disease. SCD is a serious lifelong disorder that is characterized by chronic hemolytic anemia, acute and chronic vasoocclusive complications, and organ damage.

Public Health Implications of the National Collegiate Athletic Association Rule

Testing Athletes for Sickle Cell Trait

The original 2009 legislation requiring all incoming student-athletes to be tested before participating in athletic activities was part of a legal settlement between Rice University and the parents of Dale Lloyd, a football student-athlete whose death a day after he collapsed during a workout in September 2006 was attributed to SCT.<sup>3</sup> In June of 2009, the NCAA Committee on Competitive Safeguards and Medical Aspects of Sports adopted the recommendation that its member colleges and universities test student-athletes to confirm their SCT status if that information is not already known, as a prerequisite for participation in organized sports. Subsequently, the NCAA amended its Sports Medicine Handbook to recommend that athletics departments confirm SCT status in all student-athletes during their required medical examinations.<sup>4</sup>

In April 2010, the NCAA Division I Legislative Council decided that effective from the 2010–2011 academic year, “all incoming Division I student-athletes must be tested for sickle cell trait, show proof of a prior test or sign a waiver releasing an institution from liability if they decline to be tested.”<sup>5</sup> This is a rule, not a recommendation. The NCAA cited the 2007 recommendations of the National Athletic Trainers' Association (NATA)<sup>6</sup> and the College of American Pathologists (CAP) in making their 2009 recommendations. The NCAA, NATA, and CAP all state that athletes with SCT would not be disqualified from participation in college sports.

A critical concern with both voluntary and mandated screening for SCT as a prerequisite for participation in organized sports is protection of the rights of the individual. This includes protection of privacy and protection against actions of a discriminatory nature, such as labeling stigmatization or prevention from participation in competitive sports. With regard to the NCAA rule, the benefit of screening thousands of collegiate students as prerequisite for participation in sports is unproven and should be carefully weighed against the consequential risk of stigmatization, misinformation, and unwitting denial of access to potentially successful athletic careers for those who happen to have SCT. Such consequences would be prejudicial against students found to have SCT.

Prior to the 2009 NCAA recommendation, testing for SCT was not uncommon in NCAA Division 1-A colleges. In a 2006 survey reported by Clarke and colleagues in 2007, 59 (64%) of 92 participating colleges in Division 1 Football Bowl Subdivision were screening athletes for SCT. Of those, 44 colleges (76%) targeted screening to African-American athletes, and 9 (21%) screened all athletes.<sup>7</sup> Certified athletic trainers, strength/conditioning coaches and organized sports coaches were notified of SCT test results the majority of the time, according to Clarke's findings. Screening results were primarily used to counsel athletes with SCT about potential risks during exercise, whereas genetic counseling was provided at a substantially lesser percentage of

colleges. Of the colleges that screened, 13 (22%) reported they had directly treated athletes for a complication of SCT during exercise. Forty-seven (80%) of the screening colleges reported that they screened in order to initiate preventive measures, but of 33 schools that did not screen, 24 (73%) said there was “lack of evidence-based data supporting such screening,” and 13 (39%) thought screening was cost prohibitive.

The NCAA states in its 2009–2010 Sports Medicine Handbook:

...if screening is done, it may be done on a voluntary basis with the informed consent of the student-athlete and should be offered to all student-athletes, because sickle cell trait occurs in all populations. If a screening test is positive, the student-athlete should be offered counseling on the implications of SCT, including health, athletics and family planning. Screening can be used as a gateway to discuss specific precautions.<sup>4</sup>

Further, the Handbook suggests that knowledge of a student-athlete's SCT status “should facilitate prompt and appropriate medical care during a medical emergency.” However, even prior to the new NCAA testing policy of April 2010, many problematic aspects of the rule began to emerge.

There are two options for providing results on sickle cell screening: provision of results from prior testing or from new testing. Based on informal reports from community physicians, sickle cell centers, SCD counseling programs, and SCD community-based organizations, both options have encountered problems. In the first option, some athletic departments are encouraging families to obtain newborn screening results. Unfortunately, once the family has obtained the test results, follow-up counseling or education may be unavailable or inadequate. Research has shown that some pediatricians and family physicians do not feel competent to discuss conditions included in newborn screening panels.<sup>8</sup> Evaluation of the skills of pediatric residents in relaying newborn screening results has shown that, indeed, their explanations may be too complex for some parents<sup>9</sup> and even incorrect or misleading.<sup>10</sup> and <sup>11</sup> An additional problem is that in some states, universal newborn screening for SCD may have started too late to include all children currently of college age, or the results are available only for a limited time after newborn screening.

The option of new testing is also presenting some difficulties. Colleges are offering testing and, in order to save costs, they have selected the Sickledex, an inexpensive solubility test, which tests for the presence of Hb S (but is also positive for other less common hemoglobin variants), and therefore does not provide accurate diagnosis of SCT or other common hemoglobin disorders. Athletes who test positive on the Sickledex screening test are supposed to be referred for further confirmatory testing with a more definitive test. This approach will of course result in a missed opportunity to detect and provide counseling about other hemoglobin variants in athletes testing negative for Hb S. Thus, a negative Sickledex screening test gives athletes the false impression of having no abnormal hemoglobins.

Other barriers encountered in the college-based testing have included unavailability of coaches and athletic trainers for education sessions about SCT and exercise-related illness, responsibility for the cost of testing—college or student—and targeting of testing at some athletes and sports as a cost-saving measure.

In a more organized approach, one sickle cell center partnered with a local university to provide testing, on-site counseling, and education about SCT to student-athletes.<sup>12</sup> Testing was voluntary and included pre-test counseling with each student-athlete. Post-test telephone counseling was provided regardless of trait status. Sickle cell center staff met with coaches, athletic trainers, and administrators to provide education about SCT, methods to prevent heat and exercise-related injury, and counseling to help prevent stigmatization of student-athletes found to have SCT.

## Public Health Implications of Sickle Cell Trait

### Molecular Pathology

Red cells are loaded with hemoglobin, the oxygen-carrier chemical. Hemoglobin picks up oxygen from the air in our lungs and delivers it to tissues in the body where it is needed. Hemoglobins are made of two pairs of two different types of proteins called globins. Normal Hb A is composed of two normal alpha ( $\alpha$ A) and two normal beta ( $\beta$ A) globins. Sickle hemoglobin (Hb S) is made of two normal alpha ( $\alpha$ A) and two sickle beta ( $\beta$ S) globins. Unlike Hb A, when Hb S molecules give up the oxygen they are carrying, they begin to stick to each other to form polymers within the red cell, forcing the cell into crescent-shaped cells called “sickle” cells. Sickle cells are sticky, rigid, and can get trapped in small blood vessels and also damage large ones.

In SCT red cells, there are three types of hemoglobin, A, S, and a hybrid of A and S, designated as A/S.<sup>13</sup> Both Hb S and Hb A/S hybrid participate in polymer formation when deoxygenated. In SCT red cells, the proportions of Hb S and Hb A/S exceed that of Hb A; however, there is sufficient Hb A to inhibit polymerization, especially of Hb A/S, to a degree that ensures that SCT red cells do not sickle under most physiologic conditions. However, it is not surprising that red blood cells from individuals with SCT can be induced to sickle in vitro under certain extreme conditions such as severe deoxygenation.<sup>14</sup> Furthermore, in situations or in tissues where high plasma osmolarity, severe acidosis, and/or hypoxia occur, such as the renal medulla, sickling is believed to occur in SCT.

### Health Consequences

Sickle cell trait is known as a powerful protector of young children from mortality and severe morbidity from acute falciparum malaria infection through reduced parasite density.<sup>15</sup> In malaria endemic populations, SCT has a broad positive effect on child survival. In other populations, there is no evidence of such a beneficial effect of SCT. Among 65,514 black patients admitted consecutively to 13 Veterans Administration (VA) hospitals in the 1970s, 7.8% were found on blood tests to have SCT.<sup>16</sup> The inpatient records of 24,616 members of the tested cohort: 18,294 with no abnormal hemoglobins, 4900 with SCT, and 1422 with Hb C trait were reviewed. (Hb C is the product of the  $\beta$ C globin gene, another  $\beta$  globin gene variant. Hb C by itself does not cause sickling, but when the  $\beta$ C gene is co-inherited with the  $\beta$ S gene, the result is SCD-SC, a milder form of SCD compared to SCD-SS. People with Hb C trait (AC) are healthy but can pass on the  $\beta$ C gene to their offspring.) The VA study concluded that “sickle cell trait had no effect on average age at hospitalization or death, overall mortality, length of hospitalization on medical and surgical wards, and frequency of any diagnosis, except essential hematuria and pulmonary embolism.”

Although, historically, SCT has been considered as an asymptomatic condition, hyposthenuria,<sup>17</sup> hematuria,<sup>18</sup> and an increased risk for glaucoma after traumatic hyphema are now accepted as complications of SCT.<sup>19</sup> In addition, splenic infarction has been reported in individuals with SCT at high altitudes.<sup>20</sup> Over the last 2 decades, renal medullary carcinoma, a rare aggressive kidney tumor, has been reported to be associated with SCT.<sup>21</sup> Recent studies and reports have linked other adverse health outcomes to sickle cell trait that have not yet been scientifically confirmed.<sup>22</sup>

There has been growing concern over the past several decades about the association of SCT and exercise-related morbidity and mortality in collegiate athletes and military recruits. The strongest

epidemiologic data supporting that association was from a study of over 2 million military recruits in which the risk of sudden unexplained death in recruits with SCT (Hb AS) was compared with that in recruits without Hb S.<sup>23</sup> The retrospective review of 1977–1981 demonstrated that among black recruits, those with SCT (AS) were 27.6 times more likely to suffer sudden unexplained death than those without Hb S; and, among all recruits (black and nonblack), those recruits with SCT were 39.8 times more likely to suffer sudden unexplained death than those without Hb S. Over the 5-year period reviewed, there were 12 unexplained sudden deaths in 37,300 black recruits with SCT, none in 1300 nonblack recruits with SCT, and 5 in 429,000 black and 11 in 1,617,000 nonblack recruits without Hb S. All the 12 sudden unexpected deaths in recruits with SCT were related to exercise, and five of the 12 were classified as “sudden unexplained cardiac deaths.”

The retrospective report by Kark et al.<sup>24</sup> from the U.S. military suggested strongly that exertional heat illness might account for increased incidence of sudden death in military recruits, especially those with SCT, who were training under extreme conditions. In a 10-year (1982–1991) follow-up prospective trial of a modified training regimen that included enforced hydration and close monitoring of environmental conditions, there was an overall decrease in sudden expected deaths among the 2.3 million recruits, with none occurring among the roughly 40,000 recruits with SCT.<sup>24</sup> Training centers not participating in the trial had rates of sudden unexpected deaths similar to those reported in the 1977–1981 review. Based on this study, testing for SCT was removed as a requirement for U.S. Army accession in 1996. There have not been similar epidemiologic studies or intervention trials in collegiate or any other group of athletes.

However, although exercise-related injury and death are rare generally, there continues to be concern over the concentration of deaths among athletes with SCT. The issue of how to manage exercise in people with SCT has been debated in two articles that summarize much of the debate.<sup>25</sup> and <sup>26</sup> There have been a few reports of sudden deaths in college athletes with SCT over the last 15 years. These cases have received a great deal of media attention. Because there is no systematic reporting or registry of exercise-related deaths, and in the press accounts, the basis for the diagnosis of SCT is often unclear, the true incidence is unknown. Since many of these cases were settled out of court, the medical details have neither been revealed nor subjected to scientific review. Without well-designed epidemiologic studies, the number of deaths and injury, their causes, possible underlying pathophysiologic mechanisms, and true attributable risks in individuals with SCT remain unclear.

However, there are common clinical themes. Many of the deaths occurred after strenuous exercise in unconditioned military recruits or deconditioned athletes in pre-season. Some reports suggest that milder episodes of heat-related illness occurred previously in the subjects.<sup>27</sup> Clinical description of fatal cases are often incomplete and anecdotal. The exercise routine leading to the acute illness is often easier to document in organized athletic activities. It has been suggested that increased risk of morbidity/mortality is related to repeated exercise with great physical effort over a short period of time rather than sustained mild to moderate physical effort over a long period.

Finally, experts do not agree on the possible underlying pathophysiologic mechanisms that may lead to sudden death in individuals with SCT who undergo strenuous exercise. Some believe that red cell sickling is the primary event leading to vascular occlusion, muscle infarction, and rhabdomyolysis.<sup>22</sup> Almost all reports of unexplained death in people with Hb S cite the presence of sickled red blood cells at autopsy as causation of death. However, the presence of sickled cells in postmortem tissue specimens from a person with Hb S does not imply pre-mortem sickling. In fact, the tissue hypoxia and acidosis associated with death are expected to induce deoxygenation and polymerization of sickle hemoglobin and red cell sickling soon after death. Therefore, sickling seen in postmortem samples is most likely an artifact of death. Hyposthenuria, a known feature of SCT, has been suggested as a factor that may increase the risk of dehydration leading to rhabdomyolysis. Sickling of a few red cells has been observed in experimental subjects with SCT undergoing strenuous exercise under conditions of heat and restricted hydration.<sup>28</sup>

Athletes with SCT can and have performed at the highest level of sports. A report regarding athletes in the National Football League demonstrated that the prevalence rates of SCT were similar to those in the general population.<sup>29</sup> In addition, exercise in individuals with mild or severe forms of SCD does not seem to be associated with serious adverse outcomes, making a biological link between sudden death and sickling much more difficult to suspect in those with SCT. However, those with the most severe forms of SCD may be incapable of or prohibited from participating in strenuous exercise to the degree where adverse outcomes may be seen.

In summary, there is evidence for the occurrence of exercise and/or heat-related acute illness in people with SCT. Some of these events are severe and fulminant enough to cause death. However, the prevalence of exercise-related illness and death in people with SCT is too small to affect the overall survival or morbidity of the condition. The possibility that an unidentified, rare, genetic defect found in a subset of people with SCT is either solely or partially responsible for the increased risk of exercise and/or heat-related death can be ruled out only through well-organized, large-scale genetic epidemiology studies.

## Management of the Student Athlete with Sickle Cell Trait

The NCAA recommends that student-athletes with SCT should “set their own pace”; engage in slow and gradual pre-season conditioning; use adequate rest and recovery between repetitions; be excused from some performance tests; stop activity when struggling or experiencing symptoms such as muscle pain, abnormal weakness, undue fatigue or breathlessness; stay well hydrated, especially in hot and humid conditions; refrain from extreme exercise when ill; access supplemental oxygen at (high) altitudes when needed; and seek prompt medical care when experiencing unusual distress.<sup>4</sup>

These guidelines place the burden on the athlete to design his/her own training program and monitor his/her condition during strenuous activity. However, athletes do not usually design their own training schedules or exercise routines. On the other hand, the guidelines do not address the potential of the coach to limit the practice or play time of the athlete with SCT, consciously or unconsciously, out of concern for the safety of the athlete or for potential liability. The guidelines also do not address the culture of competitive sports by which athletes are pushed beyond their limits and those who cannot keep up are not given the same opportunities. Guidelines to prevent dehydration and exercise-related illness for all student-athletes similar to those instituted by the Department of Defense have not been recommended by the NCAA.<sup>30</sup>

Formal responses from the SACHDNC, the Sickle Cell Disease Association of America, Inc., and the American Academy of Pediatrics (AAP) to the NCAA rule do not support carrier screening as a means to reduce heat-related illness or death. The editorial by Hord and Rice in the AAP newsletter indicated that the risk of illness will be reduced for all individuals as training and fitness standards are modified.<sup>31</sup> The authors noted that successful training modifications have occurred in military, firefighter, and police trainee programs. Continued assessment and modification of collegiate training protocols, development and implementation of educational and awareness programs, and a clear chain of administrative responsibility to actively address illness and injury prevention will benefit all athletes.<sup>31</sup>

The SACHDNC has developed a report to advise the Secretary of the USDHHS about the 2010 rule of the NCAA requiring testing for SCT in all incoming Division I student athletes, and called for evaluation and screening for SCD and other genetic conditions taking place within the individual's medical home where they receive individualized comprehensive care. Evaluation should include counseling regarding the implications of the information for the individual and

assurance of the privacy of genetic information. In addition, SACHDNC advised the Secretary, HHS that as part of the individual's annual medical evaluation for participation in sports, all potential athletes should receive education on safe practices for prevention of exercise and heat-related illnesses.

## Genetic Privacy

Genetics and genomics have provided the ability to reveal the “invisible” part of heredity at the molecular level.<sup>32</sup> Sickle cell disease, the first “molecular disease,” has provided a case study for the exploration of the legal, ethical, and social implications of genetic screening programs. Mandatory screening programs, as a condition for school attendance and marriage licenses, are a part of the history of sickle cell screening. Many sickle cell screening programs in the late 1960s and 1970s were later judged shortsighted, with limited or no benefit.<sup>33</sup> The history of sickle cell testing has been fraught with abuse of human rights, including the modern right to genetic privacy, with examples of individuals being screened for SCT without their knowledge.

In response to the case of *Norman-Bloodsaw v. Lawrence Berkeley Laboratory*, in which employees were tested for SCT, syphilis, and pregnancy without their knowledge, and other examples of invasion of genetic privacy, many states enacted genetic privacy and nondiscrimination laws.<sup>34</sup> In the case of student-athletes, mandatory identification of sickle cell status, not only discloses information about the individual athlete, but may also disclose information about paternity and genetic carrier status of family members, raising important privacy and consent issues, such as: Is an athlete's right to genetic privacy invaded if the athlete is required to undergo a test to determine sickle cell status?

## Genetic Discrimination

Before 2008, a patchwork of state law was enacted addressing employment and insurance discrimination and genetic privacy rights. On May 21, 2008, President Bush signed the federal Genetic Information Nondiscrimination Act of 2008 (GINA).<sup>35</sup> The congressional findings published in support of the law highlighted the mass screening of African Americans for sickle cell carrier status and the resulting discrimination that occurred during the 1960s and 1970s as a rationale for GINA.

The reach of GINA is limited to employment and health insurance discrimination. GINA specifically excludes the military, where historically, there have been examples of genetic

discrimination against individuals with SCT.<sup>36</sup> Covered entities include health insurers and employers; organizations such as the NCAA are not explicitly covered.

The Genetic Information Nondiscrimination Act of 2008 became effective on November 21, 2009. A limitation of the legislation is that GINA prohibits discrimination based on genotype, but not phenotype.<sup>37</sup> Thus, GINA applies only to individuals who are asymptomatic (nonmanifested condition). However, the current debate that SCT is associated with substantial clinical indications during intense exercise can be argued as establishing a manifested genetic condition and excluded under GINA.

A number of ethical, legal, and social questions have been identified regarding the NCAA carrier screening rule.<sup>38</sup> The resounding unanswered question is whether existing medical and public health data used as the basis of this mandate have been interpreted and applied appropriately. The best answers may lie within well-designed epidemiologic and clinical research to better understand the cause of and risk factors for rare deaths of athletes with SCT. This research should be conducted within a framework that incorporates lessons learned from the unfortunate historical legacy of some public health SCT screening programs. In addition, implementation of the SACHDNC's recommendations will move the discussion of carrier screening to a public forum where there will be ongoing monitoring of the impact of screening on organized sports.

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Recommendations from the Secretary's Advisory Committee on Heritable Disorders in Newborns and Children (SACHDNC) can be reviewed at the following website: <http://www.hrsa.gov/advisorycommittees/mchbadvisory/heritabledisorders/recommendations/correspondence/sicklecell061410.pdf>. The SACHDNC's recommendation to the Honorable Kathleen Sebelius can be found in Appendix A (available online at [www.ajpmonline.net](http://www.ajpmonline.net)).

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