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Sickle cell disease: The intersection of culture, medicine, and technology and eHealth perspectives

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A few centuries ago the Greek physician Hippocrates suggested that medical health and temperament was based on the balance of four "humors" or bodily fluids including blood, yellow bile, black bile, and phlegm. The theory of "*humorism*" suggested that individuals differed in the composition of these bodily fluids, giving rise to temperament or individual differences in emotions, mood, and behavior. Nobody is quite sure of where the concept of "four" humors originated, however, the way blood clots in its natural form may have contributed to the idea of four layers*. The influence of "humoralism" on the practice of medicine lasted up until the 19th century at which point both cellular pathology and chemistry patently discredited the theory.

Moving forward from the Greek's vision of health and well-being, in the current issue of LARS eNEWS we examine one of the four humors, blood, directing our attention to the most pernicious of blood diseases, sickle cell disease (SCD). We provide an overview of the disease including its epidemiology, clinical course, and treatment. Consistent with our focus on the marriage between technology and behavioral health, we then discuss the steps required to bring SCD treatment into the fold of *eHealth*. This supports our emphasis on promoting state-of-the-art *eHealth* technology that can be used in the treatment of chronic diseases, social problems, and advancing the health of our nation.

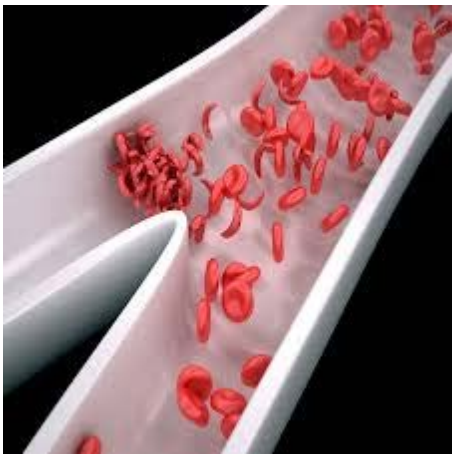
Background Information

SCD, the most prevalent inherited monogenic blood disorder in the world, affects millions of people but is most common in areas of the world where the mosquito born parasite *Plasmodium falciparum* (malaria) is also present. The sickle cell trait (the heterozygous state) confers some protection against the malarial parasitization of red blood cells especially during early childhood†. This accounts for its high frequency in tropical

* The notion of four "layers" can be attributed to the Swedish physician Robin Fåhræus (1921) who devised the erythrocyte sedimentation rate. He indicated that when blood is drawn into a glass container and left untouched for about an hour, four different layers will appear to the naked eye. A dark clot forms at the bottom (the "black bile"). Above the clot is a layer of red blood cells (the "blood"). Above this is a whitish layer of white blood cells (the "phlegm"). The top layer is clear yellow serum (the "yellow bile").

† The precise mechanism for this natural selection protection is unknown, but may include phagocytes eliminating the sickle cell carrying the parasite because infected cells have lower oxygen tension reduced by the parasite and also sickled cells produce toxins (anion and hydrogen peroxide) to the parasite.

regions. The Global Rural-Urban Mapping Project estimates an annual worldwide birth of more than 312,000 newborns with the homozygous (SS) form of the disease, mostly found in sub-Saharan Africa, the Arabian Peninsula and India[1].



Sickle cell disease is a genetic disorder that affects hemoglobin in the blood. It results from a mutation in the β-globin gene and is inherited in an autosomal recessive pattern. A person who carries one copy of the mutated gene is said to be a healthy *carrier* or to have the sickle cell trait. Mendelian genetics teaches us that when 2 people are carriers of the autosomal recessive gene, there is a 25% (1 in 4) chance/bad luck that the child will have SCD (SS), 50% probability that the child will be a carrier (AS) and 25% chance of having no mutated gene (AA). SCD was first described clinically in 1910 in a report published by James Herrick[2]. Herrick encountered a blood smear taken from a West Indian dental student living in Chicago suffering from anemia. Under microscopic examination he saw a "peculiar elongated and sickle-shaped red blood corpuscles." He then linked the clinical symptoms to the abnormal erythrocytes. In 1917, Emmel's discovery of the in vitro sickling phenomenon in several members of the same family suggested for the first time a genetic basis for sickling[3]. SCD was thus understood as an inherited disease. Later research led to the discovery that the sickling was inherited as a Mendelian autosomal recessive pattern, which means that both copies of the gene have mutations (SS gene) and that the sickling was due to erythrocyte oxygen deprivation[‡]. In 1949 Linus Pauling named the disease, after observing that sickle cell and normal adult hemoglobin behave differently when their carbon monoxide derivatives are subjected to electrophoresis at a neutral pH. Shortly thereafter Ingram (1957) identified the molecular structure of the sickle hemoglobin.

The sickling of normal red blood cells commonly causes symptoms as early as childhood (around 6 months – 1 year). Among the many sequelae of the sickling process and the abnormal adhesion of sickled red cells to the vascular endothelium are anemia, jaundice, and painful episodes referred to as vaso-occlusive crises. Many individuals experience severe cramping, fatigue, body aches, and also dactylitis, a condition noted by excessive swelling of the hands and feet. Since red blood cells are instrumental in the transport of oxygen, any deficiencies or deprivation of oxygen to tissues or organs can lead to life threatening damage, especially in the lungs, kidneys, spleen and brain. These symptoms are unpredictable, can be extremely serious and even life threatening. Moreover, the same individual, over the course of his or her lifetime, may have asymptomatic periods or periods of serious symptomatic manifestations of the disease. A child, symptom free from birth can have a serious life-threatening crisis with no previous warning. As recently as 1994, the average life expectancy of a person suffering from the debilitating SS form was 42 years for men and 48 years for women. Most sickle cell disease patients live in low-income countries and socioeconomic factors are undoubtedly important, but there is a dearth of research beyond documenting that sickle cell disease is associated with lower socioeconomic status.

Treatment Progress. Over the past 100 years since the disease was first identified, research and clinical practice have led to an increased understanding of SCD accompanied by a decrease in morbidity and mortality. Unfortunately, other than bone marrow transplant[§] there is still no cure for SCD. Today, implementation of neonatal screening has led to prophylactic comprehensive treatment plans initiated from the time of the initial diagnosis. As a result, patients may have a nearly normal quality of life and an increased life expectancy. The systematic health care for SCD in the US includes prophylactic antibiotic treatment from infancy until 5 years old, folic acid supplement, pneumococcal vaccination, parent education and in the case of severe symptomatology the use of hydroxycarbamide 64 or blood transfusion.

Interestingly, SCD is classified as a rare disease by the US Department of Health and Human Services despite the fact that 1 in every 400 African-American newborn is affected[6]. In the US alone, there are between 104,000 – 138,900 individuals suffering from the disease based on birth-cohort prevalence[7]. The disease creates tremendous drain on the healthcare system with increased hospitalizations (treating pain crisis) and annual costs estimated upwards of $475 million[**]. Moreover, an additional 3.5 million people are heterozygous carriers of the sickle cell trait (HbS).

Cultural Aspects of SCD. SCD cannot be treated in the same way as many other chronic diseases (i.e. asthma, diabetes, obesity). Before discussing *eHealth* applications for SCD, it is essential to understand the unique factors that interact and distinguish SCD with its gene mutation, an "encultured gene," from all other chronic diseases[9]. The cultural context includes symbolic representations of the disease as well as socio-economic and racial issues that all play a part in the elaboration of feasible treatment plans. SCD is an example of how race and culture both intersect with science and the lasting effects and repercussions for this disease, often stigmatized as a "black disease." It was not until 1972 that SCD came to public attention with a series of Senate hearings resulting in the passage of the Sickle Cell Anemia Control Act of 1972[10].

Blood has long fascinated the public with its inherent symbols, rituals and myths, many of which are still common today (i.e., up until the 19th century people drained blood using leeches to empty the human corpus of sickness)[11]. In the US, the concept of bad blood and its possible infiltration into white bodies gained support and affirmation with

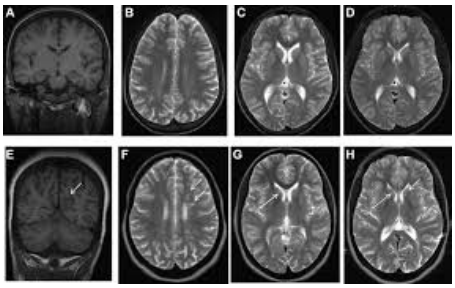
‡ Technically speaking, normal red blood cells (erythrocytes) have a deformability characteristics that lets them "squeeze" into small microcirculatory capillaries in the blood system, particularly those that feed organs and muscle. Under low oxygen tension, red blood cells in individuals with sickle cell disease don't deform as well and "sickle" (polymerize), indicated by the crescent shape. This deformity leads to acute rhabdomyolysis and necrosis within the muscle tissue, causing release of the protein myoglobin into the bloodstream that causes damage to the kidneys and other organs.

§ A bone marrow/stem cell transplant is indicated when a Human Leukocyte Antigen-matched donor can be found. There is some risk of mortality (~3%). In some cases, where no HLA matched donor can be found, a haploidentical mother to child (mismatched donor) can be used, although one RCT has shown a relatively high mortality rate of 7% from bone marrow transplant [Sodani, P., Isgrò, A., Gaziev, J., Paciaroni K., … Lucarelli, G. (2011). T cell-depleted hla-haploidentical stem cell transplantation in thalassemia young patients. Pediatric Report, 3(s2) e13].

** Previously cited, Cheng. p. 2279.

the discovery of the sickle cell and its frequency in people of African origin. SCD is often a taboo and a source of shame for those affected who are of African ancestry or who identify themselves as "black." In African countries, the low survival rate (frequent death before 5 years old) and average life expectancy (20 years), the severity of the symptoms beginning in early childhood, and the organ complications surfacing in adulthood contribute to an overwhelming and often unspoken fear of death and ensuing depression for patients living in the US or Europe.

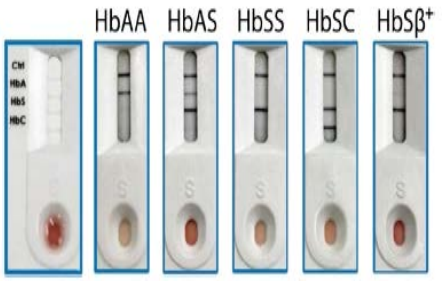
Pain and SCD. SCD disease is characterized by chronic hemolysis, vaso-occlusive pain, and functional asplenia, and individuals with SCD have a very high rate of pneumococcal infection. Many patients suffer from acute chest syndrome, bone infarcts, and have their spleen removed early in life. However, it is the symptom of body and visceral pain that receives the most attention in the clinical and research community. The excruciating joint and bone pain from vaso-occlusive crises (VOC) are intolerable for patients as well as their parents and entourage. In many cases, it is also hard for medical professionals, who are often left "powerless" to treat patients other than administering high doses of pain analgesics (i.e., opioids like morphine). The occurrence of painful VOC episodes are unpredictable regarding their onset, frequency, intensity or duration. Research studies document that every child spends an average of 1 week/year hospitalized for a vaso-occlusive episode or related complications. With increased access to systematic magnetic resonance imaging (MRI) in pediatric care, studies show that 25% of those suffering from SCD will have a neurological complication over their lifetime and often occurring in early childhood.



The silent ischemia or silent infarcts (shown in the MRI above) present a real challenge for development of treatment plans. Very young children with sickle cell anemia (and no history of clinical stroke) have infarction in the brain and/or stenosis of major cerebral arteries, like those reported in older children. These findings indicate a need for larger studies to define the incidence of CNS lesions in this age group and to determine the need for early therapeutic intervention to prevent CNS complications (i.e. cognitive impairment). Along with a growing literature that documents associations between neuro-cognitive impairment and silent infarcts, there is now also growing concern that multiple linguistic and socio-cultural factors influence cognitive functioning and may carry more weight than traditional complications associated with the disease. For instance, a family's cultural representation of SCD and their emotional response to the disease can be as destructive as a silent cerebral infarct. One way to tease apart cultural and familial factors from negative disease sequelae involves using non-affected siblings as control groups. Overall, this type of study has found that siblings have higher cognitive performance[††].

Treatment Care for SCD. The paradox of SCD is that there is no "*disease-modifying treatment*" as we encounter with most other chronic diseases. In children, apart from unpredictable vaso-occlusive crises, SCD is asymptomatic and prophylaxis is the standard treatment. No proven methods prevent either sickle cell crises or long-term complications (organ damage etc.). There are however factors known to set-off the crises. Excessive exercise, cold temperature and high altitude (skiing) must be avoided. After diagnosis, the most important precaution is increased fluid intake. Children are encouraged to drink 1 ½ - 2 liters of water/day and must be allowed to drink during class and access the toilet when needed.

The most significant measure taken in the last 15 years is systematic newborn screening (NBS) for SCD. Hemoglobinopathy newborn screening primarily uses isoelectric focusing, which can produce results in a quick fashion. Early diagnosis allows doctors to immediately provide prophylactic dosage of antibiotics to babies with SCD (polyvalent pneumococcal 13-valent vaccine [Prevnar®, PCV13]), which helps to prevent life-threatening infections. National or regional hemoglobinopathy NBS programs have been implemented in many industrialized countries and in many developing countries such as in the island of Guadeloupe, Jamaica, Ghana, Angola, and the Democratic Republic of Congo and Burkina Faso.

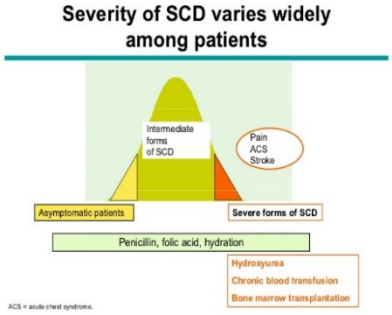


The Sickle SCAN is a novel Point of Care (POC) for the detection of hemoglobin (Hb) A, S, and C and may augment public health initiatives in low resource populations. The test uses lateral flow technology, requires 5 µL of blood (fresh or dried blood) to be added to a buffer-loaded module that will hemolyze the erythrocytes. The hemolyzed solution is dropped onto the sample inlet of the Sickle SCAN cartridge, at which point the sample flows through, interacting with antibody-conjugated colorimetric detector nanoparticles, and travels to the capture zones. There are four possible detection lines: Hb A, S, C, and a control line. This testing procedure has been validated in children over one year of age.

Like any novel innovation, the POC Scan or even IEF technique requires capacity building to strengthen the infrastructure required to sustain NBS before and during the initial introduction and implementation in underserved regions of the world. Capacity

[††] Unfortunately, the design of these studies cannot discern whether there are differences in the amount of attention a parent pays to the sickle cell child versus how much they spend with a non-affected child. Many twin or "genetic" familial transmission studies suffer from the same problem, which amounts to teasing apart and reliably assessing the emotional tone of a parent directed toward one child versus another.

building is needed to promote cooperation and build support among the diverse health and administrative units that have purview over NBS; in other words,



developing the human, physical, technological, and information resources and local expertise needed to integrate NBS into routine medical and wellness operations. This includes finding "*program champions*" in rural and underserved (or resistant) communities to educate healthcare policymakers to promote NBS worldwide.

There are two treatments used for severely symptomatic SCD; hydroxyurea and blood transfusion. Hydroxyurea, increasingly prescribed in the standard treatment plan, is an oral medication, originally used in oncology, which is used to increase fetal hemoglobin (HbF) in the body. The total hemoglobin is thus increased and the fetal hemoglobin is used by the body to promote healthy blood cells and reduce the risk of cells sickling. New protocols encourage the systematic prescription for children from the age of 2 years old without considering that hydroxyurea can negatively impact fertility. Blood transfusions with their ensuing risks, provide new blood with healthy red blood cells and oxygen to the body. Transfusions can thus reduce the amount of blockage that can occur with the sickled cells and are prescribed when a high risk of stroke exists.

Two known cures include bone marrow transplant and genetic modification therapy:

- Bone marrow transplant, is only possible in childhood (before 16 years old) for a small number of patients with a compatible donor. When successful, SCD is cured but the DNA of the patient is not changed and he/she remains a potential transmitter of the disease.
- Genetic modification therapy offers hope for the future but is still experimental. In March 2017, a French team reported the first success of gene therapy for a teenage boy in the New England Journal of Medicine[12]. This breakthrough provides proof of concept for this approach and may help to guide the design of future clinical trials involving gene therapy for sickle cell disease.

Although medical treatment priorities are clear[8], few recommendations emphasize self-management, patient education, psychological support, patient support groups, alternative medicine or e-medicine. A US government report highlights the dearth of research in the field:

"*The process of developing guideline for the management of children, adolescents, and adults with SCD has been challenging because high-quality evidence is limited in virtually every area related to SCD management. The systematic review of the literature identified a very small number of RCT's (randomized clinical trial) in individuals with SCD, demonstrating the extensive knowledge gaps in sickle cell education and care of affected individuals.*"

Treatment of Pain. Excruciating pain is the hallmark symptom of SCD. In many African languages, the name attributed to the disease refers to the "pain that grinds the bones." Pain is treated symptomatically first by hyperhydration either orally or delivered intravenously, rest and analgesics (Grade I to III). High doses of morphine for the pain are commonly administered but a recent study suggests that high doses may be responsible for organ damage often found in SCD patients[13].

Pain management is where psychological support, therapy and the development of e-medicine can play an important role in future treatment care. Already, existing studies of "self-management" and pain control have informed health professionals that many SCD patients feel excluded and isolated. The poignant interviews conducted by French clinical psychologist Eliane Raffet provide a touching testimony of the parents' and children's distress when confronted with SCD[14]. She also highlights the gap between the scientific explanation of genetic transmission and the parents' desire for less "scientific" explanations. In many cultures from North Africa, Haiti, Jamaica and other less westernized countries, the disease is commonly attributed to sorcery, a spell cast by a member of the family, a curse, or the mother's fault as the sole person responsible for the transmission of the disease[15].

Self-Management and SCD. There has been a burgeoning interest in applying self-management strategies to the care of SCD[16]. For the most part, with youth and young adults, skills training emphasizes coping and self-control strategies to deal with pain.[‡‡] In many cases, self-management is limited to a structured education protocol neglecting the complexities of SCD. A more satisfactory approach to achieve a true improvement in quality of life (QOL) depends on a process initiated to bring about order in the lives of those suffering from SCD and their families. The acute pain from a "crisis" causes psychic disorganization, loss of identity or what is colloquially termed "falling apart"[16]. For many SCD patients, the intense pain brought on by VOC generates massive anxiety, a feeling of helplessness and incipient fear of death. Although there is implicit recognition of the importance of multi-disciplinary approach and psychological support in SCD care, there are few evidence-based studies reporting the efficacy of psychological therapies in SCD. A recent French study showed that a clinical psychologist working in tandem with the pediatric specialist can enhance cognitive functioning[17].

Innovations for SCD Treatment. Isom et al. document that only a handful of studies have used mobile applications to support self-management with SCD patients[18]. Indeed, these authors identified only 25 relevant papers that cover this subject, which pales in comparison to the numbers of individuals living with SCD. The few studies included in the literature review usually report positive outcomes. Kwateng suggests that the lack of

[‡‡] We define self-management as the active coping strategies that individuals with chronic disease incorporate into their lives to effectively deal with the medical and physical consequences and behavioral complications of illness.

clear and productive research investment is the underlying association between SCD and the black population[19]. The few publications available show original initiatives and promising results and certainly could be further developed in the future. Formative studies indicate that SCD patients are generally dissatisfied with their health care and express a desire for better care. They are open to improving their general knowledge about SCD and to the use of Information and Communication Technology (ICTs) to support their self-management needs.

McClellan and colleagues[20] provided evidence that the use of "*handheld wireless technology*" for home-based sickle cell care has significant potential as a practical model to improve symptom monitoring and communication between patients and health care professionals especially in rural or outlying regions.

Treatment for Adolescents. No satisfactory care program has been developed for the critical period of adolescence and the difficult transition from pediatric medicine to adult units. In general, the transition period for many diseases like SCD is problematic as many youth fall through the cracks and lose traction in terms of their medical care[21]. This is an area where e-medicine has significant potential for future applications as this age group is familiar with and a major consumer of electronic equipment (digital tablets, laptops, smartphones, etc.)[22]. The introduction of mobile health (mHealth) technologies seems particularly adapted to meet the challenge of adolescent health and the successful management of the transition from pediatrics to adult services[23].

Cheng et al.[6] describe an iACT system that allows "care providers to effectively and easily manage, monitor and communicate with adolescents outside of the hospital environment." Although their system has not yet been evaluated, it could provide an interesting alternative for psychotherapy for adolescents who often reject traditional approaches. The most accessible tool that is already part of numerous treatment plans is SMS text messaging. Two interesting examples that utilize this technology are a web-based diary and a text messaging service for youth. Both provide services for monitoring pain symptoms and both helped to improve the physical and mental health-status of patients[24-25].

Quantified-Self Movement and SCD. Some patients are willing to engage in Quantified-Self (QS) moving that can monitor self-tracking parameters like physical activity, diet, health status or physiological data. Like any "wearable" device, the data "tracked" allows both patients and providers to gain an increased awareness and understanding of the self. For example, people can use wearable devices to collect data or even have an "embedded system" of tracking. One program tracks the school attendance of adolescents with SCD and thus aims to reduce school absenteeism[26].

In the case of individuals living with SCD, self-monitoring can provide a wealth of information for predictive analytics using health parameter like tiredness, low blood oxygen, fast heart rate, difficult breathing or dehydration. All of these health parameters can lead to early detection of VOCs. Importantly, these data could even be hooked up to an alert system that will advise patients to seek a medical consult. This level of automation could help prevent the triggering of crises or lay the foundation for patients to seek counsel and advice that can promote behavior change and a healthier lifestyle.

Conclusion. Dampier and colleagues have shown that the majority of adults living with SCD have substantial impairment of health-related quality of life (HRQOL)[27]. For the most part, present-day treatment plans do not respond to the medical and psychosocial needs of SCD patients. Dampier et al. resoundingly call for more effective treatment of persistent pain and depression. A better understanding of the relationship between patients and their environment may allow significant improvements in health, first by giving simple medical advice and second by facilitating the development of appropriate public health policies introducing the use of *eHealth* protocols into the regular treatment care plan for SCD. As discussed, patients with SCD have multiple needs involving family, cultural, medical, and educational levels of influence. Mobile applications can provide information to patients about their disease; however, when developing mobile applications and implementing them, it is important to remember that there is a "digital divide." Access to mobile devices is not a worldwide phenomenon, nor do many individuals affected by poverty have access to the type of plans that can handle downloads, graphical interface, and unlimited Internet use[28-29].

Also key to the use of technology is recognizing there is often a "mismatch" between patient education materials about SCD and the literacy level of their intended audience[30]. Lower SES African-Americans living with SCD in the US, for instance, do not have unfettered access to technology or medical care. In general, the literacy level necessary to access available health information exceeds the reading skills of most US adults. More specifically, 35% of the African-American population score below Level 2 in literacy tests[31] – a major handicap for the implementation of e-medicine. The tools developed and the language used must be adapted to fit the population in question, which has a low level of literacy. The opportunity is immense to develop ICTs to support the self-management needs of patients with SCD and to bridge the gap between the haves and the have nots. But can the necessary funding be found? Overall, sickle cell research has historically been severely underfunded when compared to other genetic disease counterparts[§§]. The disparities in funding once again exemplify the social and political ramifications when a disease is associated with race. It is thus imperative to develop cost-effectiveness approaches that will be well received by the target audience. Without this information, policy makers will remain reluctant to fund if they have doubt about the good use of increasingly limited health care resources.

[§§] The current 2017 appropriated budget of the National Heart, Lung, and Blood Institute (NHLBI), which funds most of SCD clinical studies and translational research in cardiovascular, lung, and blood diseases is $3,115,538,000. By comparison, the budget of the National Cancer Institute (NCI), which funds cancer related research and clinical studies of smoking and tobacco use is $5,389,000,000.

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LARS Research Institute is dedicated to assisting members of the scientific community develop, implement, and evaluate comprehensive, evidenced-based Internet, clinic, school- and community-based behavioral interventions. Our portfolio includes offering services in the fields of drug and violence prevention, chronic disease self-management, and professional development/training for healthcare professionals and community health workers. We strive to improve our nation's healthcare systems by disseminating proven, evidence-based programs using rigorous scientific methods, applying state-of-the-art implementation methods, and adhering to industry standards supporting high quality program evaluation using state-of-the-art statistical techniques. Our goal is to create positive health outcomes and psychological benefits for individuals experiencing health disparities, and at the same time reducing the financial burden on our healthcare systems.

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