

A justice-based argument for including sickle cell disease in CRISPR/Cas9 clinical research

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Abstract

CRISPR/Cas9 is quickly becoming one of the most influential biotechnologies of the last five years. Clinical trials will soon be underway to test whether CRISPR/Cas9 can edit away the genetic mutations that cause sickle cell disease (SCD). This article will present the background of CRISPR/Cas9 gene editing and SCD, highlighting research that supports the application of CRISPR/Cas9 to SCD. While much has been written on why SCD is a good biological candidate for CRISPR/Cas9, less has been written on the ethical implications of including SCD in CRISPR/Cas9 research. This article will argue that there is a strong case in favor of including SCD. Three benefits are achieving distributive justice in research, continuing to repair the negative relationship between patients with SCD and the health-care system, and benefit-sharing for those who do not directly participate in CRISPR/Cas9 research. Opponents will argue that SCD is a risky candidate, that researchers will not find willing participants, and that the burden of SCD is low. Of this set of arguments, the first gives pause. However, on balance, the case in favor of including SCD in CRISPR/Cas9 research is stronger than the case against. Ultimately, this article will show that the historic and sociopolitical injustices that impede progress in treating and curing SCD can be alleviated through biotechnology.

KEYWORDS

benefit-sharing, biotechnology, clinical trials, CRISPR/Cas9, distributive justice, sickle cell disease

1 | INTRODUCTION

1.1 | CRISPR/Cas9

The field of biotechnology, through emerging innovative treatments and cures, is making a way towards the future curing of diseases that were once considered incurable. One of the newest biotechnologies with the possibility to reduce the burden of certain disorders through its genome editing capability is CRISPR/Cas9. The CRISPR/Cas9 genome editing system uses a single protein guided by a chimeric single-guide ribonucleic acid (RNA) to

target deoxyribonucleic acid (DNA).¹ The guide RNA finds and attaches to the specific sequence of DNA that needs to be cut or edited out. When Cas9 has been guided to the targeted part of the genomic sequence, Cas9 then binds to the virus's DNA with the help of a protospacer adjacent motif.² Lastly, Cas9 serves as scissors and cuts the DNA of the invading virus. CRISPR/Cas9 has been applied to edit the genomes of animals and human cell lines

¹Bak, R. O., Dever, D., & Porteus, M. H. (2018). CRISPR/Cas9 Genome editing in human hematopoietic stem cells. *Nature Protocols*, 13(2), 358–376.

²Ibid.

for many human diseases³ and several clinical trials for CRISPR/Cas9 have begun or are set to begin.⁴

1.2 | Sickle cell disease (SCD)

One of the diseases that is a promising candidate for CRISPR/Cas9 is sickle cell disease (SCD). SCD is a broad term for a monogenic disease that describes red blood cell disorders inherited in an autosomal recessive manner, such that defective genes making abnormal hemoglobin proteins pass from parents carrying one copy of abnormal hemoglobin gene to their children.⁵ SCD is further defined by different mutations in the *HBB* gene, which codes for making the two β -globin portions of hemoglobin (the other two protein subunits are α -globin subunits). These various mutations produce various abnormal hemoglobins that include HbS, HbC, HbD, HbE, HbO, and thalassemia. The most severe form of SCD, sickle cell anemia, occurs when a child inherits two copies of the defective hemoglobin S. Unlike the other mutations, the *HBB* gene mutations causing β thalassemia lead to very low levels of β -globin.⁶

All these SCD variants are grouped together as hemoglobinopathies. For the purpose of this article, SCD will be used to represent all disease genotypes. Sickle cell trait (SCT) occurs in one in 13 blacks in the USA. SCD affects about 100,000 blacks, with one in 365 black babies born with the disease.⁷ SCD is the most common inherited blood disorder in the USA and it occurs among Hispanics as well.⁸

Globally, about 5% of the world's population has a hemoglobin disorder including SCD.⁹ Incidence estimates suggest that about 250,000 to 305,800 babies are born with SCD in the world each year, and this is expected to rise by at least 100,000 by 2050.¹⁰

People of African and Mediterranean descent have the highest rates of SCD.¹¹ In Africa, SCD predominates in Ghana, Benin, Uganda, Gabon, Nigeria, and the Democratic Republic of Congo. Projections suggest that in the coming years the latter two countries will remain the most in need in terms of prevention and management.¹² Other areas of the world that have a significant prevalence of SCD are India, the Arabian Peninsula, South America, Central America, and parts of the Caribbean.¹³

SCD presents differently among individuals, with symptoms ranging from very mild to extremely devastating. As a result of polymerization, hemoglobin is distorted to form a rigid and inflexible sickle or crescent shape which reduces their oxygen carrying capacity.¹⁴ Sickle cells have a shorter life span in circulation and their removal leads to the anemia.¹⁵ The cells' rigidity hinders them from easily flowing through microcirculation, resulting in perfusion, tissue damage, and painful episodes known as sickle cell crises.¹⁶ The onset of a sickle cell crisis occurs when an infant's fetal hemoglobin (HbF) is replaced by an abnormal hemoglobin such as S to become HbS or O to become HbO.¹⁷ The corresponding clinical features that occur in early childhood are strokes around the age of 6 years, acute chest syndrome that can occur throughout life, blood infections, and hypersplenism. In later childhood and adulthood, necrosis of the femur, leg ulcerations, and reproductive issues such as delayed puberty and pregnancy complications can occur.¹⁸

The effects of SCD lead to a high mortality. Compared with their healthy black counterparts, blacks with SCD have 25–30 fewer years of life.¹⁹ Overall, the average lifespan for an individual with SCD is 40 to 60 years in the USA.²⁰ However, those who have HbF levels above 75% have longer life expectancies than those with lower levels.²¹

In 2014, the National Heart, Lung, and Blood Institute (NHLBI) Expert Panel provided evidence-based guidelines that covered the five topics of health maintenance, management of acute and chronic conditions, management of chronic complications, use of hydroxyurea, and blood transfusions.²² The panel recommended

³Linang, P., Xu, Y., Zhang, X., Ding, C., Huang, R., Zhang, Z., ... Huang J. (2015). CRISPR/Cas9-mediated gene editing in human triploid zygotes. *Protein & Cell*, 6(5), 363–372; Wang H., Yang, H., Shivalila, C. S., Dawlaty, M. M., Cheng, A. W., Zhang, F., & Jaenisch, R. (2013). One-step generation of mice carrying mutations in multiple genes by CRISPR/Cas-mediated genome engineering. *Cell*, 153(4), 910–918; Wu, Y., Liang, D., Wang, Y., Bai, M., Tang, W., Bao, S., ... Li J. (2013). Correction of a genetic disease in mouse via use of CRISPR-Cas9. *Cell Stem Cell*, 13(6), 659–662; Xue, W., Chen S., Yin, H., Tammela, T., Papagiannakopoulos, T., Joshi, N. S., ... Jacks, T. (2014). CRISPR-mediated direct mutation of cancer genes in the mouse liver. *Nature*, 514(7522), 380–384. Mali, P., Yang, L., Esvelt, K. M., Aach, J., Guell, M. DiCarlo, J. E., ... Church, G. M. (2013). RNA-guided human genome engineering via Cas9. *Science*, 339(6121), 823–826.

⁴National Institutes of Health (NIH) (2017). PD-1 knockout engineered T cells for metastatic non-small cell lung cancer. Bethesda, MD: NIH, U.S. National Library of Medicine. Retrieved from <https://clinicaltrials.gov/ct2/show/NCT02793856>.

⁵National Heart, Lung, and Blood Institute (NHLBI). (2017). Sickle cell disease. Bethesda, MD: NHLBI. Retrieved from <https://www.nhlbi.nih.gov/health-topics/sickle-cell-disease>; Centers for Disease and Control and Prevention (CDC). (2016). Facts about sickle cell disease. Atlanta, GA: CDC. Retrieved from <https://www.cdc.gov/ncbddd/sicklecell/facts.html>.

⁶NIH (2012). *Sickle cell disease*. p. 1. Bethesda, MD: NIH. Retrieved from <https://ghr.nlm.nih.gov/condition/sickle-cell-disease#statistics>.

⁷CDC. (2016). *Data and statistics*. Atlanta, GA: CDC. Retrieved from <https://www.cdc.gov/ncbddd/sicklecell/data.html>.

⁸Op. cit. note 6, p. 1.

⁹World Health Organization (WHO). (2017). Sickle cell disease. Retrieved from <https://www.afro.who.int/health-topics/sickle-cell-disease>.

¹⁰Lervolino, L. G., Baldin, P. E., Picado, S. M., Calil, K. B., Viel, A. A., & Campos, L. A. (2011). Prevalence of sickle cell disease and sickle cell trait in national neonatal screening studies. *Revista Brasileira de Hematologia e Hemoterapia*, 33(1), 49–54; Piel, F., Hay, S. I., Gupta, S., Weatherall, D. J., & Williams, T. N. (2013). Global burden of sickle cell anaemia in children under five, 2010–2050: Modelling based on demographics, excess mortality, and interventions. *PLoS Medicine*, 2013; 10(7).

¹¹Ashley-Koch, A., Yang, Q., & Olney R., S. (2000). Sickle hemoglobin (HbS) allele and sickle cell disease: A HuGE Review. *American Journal of Epidemiology*, 151(9), 839–845.

¹²Serjeant G. R. (2013). The natural history of sickle cell disease. *Cold Spring Harbor Perspectives in Medicine*, 3(10), 1–11.

¹³NIH, op. cit. note 6, p. 1.

¹⁴NHLBI, op. cit. note 5; CDC, op. cit. note 5.

¹⁵CDC. (2016). What is sickle cell disease? Atlanta, GA: CDC. Retrieved from <https://www.cdc.gov/ncbddd/sicklecell/facts.html>; Higgs, D. R., & Wood, W. G. (2008). Genetic complexity in sickle cell disease. *Proceedings of the National Academy of Sciences of the United States of America*, 105(33), 11595–11596.

¹⁶Higgs and Wood, op. cit. note 15.

¹⁷Op. cit. note 12, pp. 1–11.

¹⁸Makani, J., Ofori-Acquah, S. F., Nnodu, O., Wonkam, A., & Ohene-Frempong, K. (2013). Sickle cell disease: New opportunities and challenges in Africa. *Scientific World Journal*, 1–16. <https://doi.org/10.1155/2013/193252>.

¹⁹NHLBI. (2014). *Evidence-based management of sickle cell disease*. Bethesda, MD: NIH. Retrieved from https://www.nhlbi.nih.gov/sites/default/files/media/docs/sickle-cell-disease-report%20020816_0.pdf.

²⁰NHLBI. (2016). Sickle cell disease. Bethesda, MD: NIH. Retrieved from <https://www.nhlbi.nih.gov/health/health-topics/topics/sca>.

²¹Platt, O. S., Brambilla, D. J., Rosse, W. F., Milner, P. F., Castro, O., Steinberg M. H., ... Klug PP. (1994). Mortality in sickle cell disease. Life expectancy and risk factors for early death. *New England Journal of Medicine*, 330(23), 1639–1644.

²²Op. cit. note 19.

the following: prophylactic penicillin for children up to the age of 5, folic acid, all vaccinations according to the Advisory Committee on Immunization Practices' harmonized immunization schedule, general clinical preventative care in line with the US Preventative Services Task Force's General Recommendations, hydroxyurea for adults with frequent, debilitating crises, and blood transfusions before surgery or as indicated by a physician.²³ Recommendations for maintaining health also include a healthy diet, sufficient rest, physical exercise, and avoiding overexertion.²⁴

1.3 | CRISPR/Cas9 and SCD compatibility

While there is no standardized cure for SCD, patients with severe SCD who do not respond to any other treatments or lifestyle changes may undergo bone marrow transplants to alleviate or eradicate symptoms. In a longitudinal study that investigated the aftermath of bone marrow transplantation for symptomatic SCD, researchers found that there was a 94% survival rate and 84% event-free survival.²⁵ Furthermore, not only were patients cured of SCD, but the incidence of strokes disappeared, and all but one patient reported a score of 100% for their quality of life after transplantation.²⁶

A major strength of bone marrow transplants is that individuals cured of SCD emerge as if they had never had SCD before, and the complications caused by their blood producing crescent-shaped cells are eliminated.²⁷ While some individuals may need hydroxyurea treatment for some time, they are still asymptomatic.²⁸ The key factor to eliminating the symptoms of stroke, pain, and acute chest syndrome that patients face before transplantation is stable donor engraftment.²⁹ While bone marrow transplants have been a success, the risk of graft-versus-host disease and rejection of the host marrow is significant.³⁰ With CRISPR/Cas9 the risk of graft-versus-host disease is eliminated since these are autologous transplants.³¹

SCD is considered a therapeutic target for the gene editing ability of CRISPR/Cas9 because it is a monogenic recessive

disorder that is caused by a substitution in the β -globin gene that alters one amino acid.³² Using established methodology, CRISPR/Cas9 has been used to edit genomes of human induced pluripotent stem cells (iPSCs) as a way of providing gene-corrected cells for SCD.³³ The results have been encouraging, based on the *HBB* protein expression, thus suggesting that CRISPR/Cas9 genome editing of SCD iPSCs could be used for disease modeling and potential gene therapy.³⁴ Following reports of the curative strategy using CRISPR/Cas9-mediated *HBB* targeting for hematopoietic stem cells in SCD disease patients and other β -hemoglobinopathies, there is increased confidence of clinical trials using the method of ex vivo gene correction followed by autologous transplantation.³⁵

Theoretically, CRISPR/Cas9 could be used to treat SCD by insertions or deletions at the fetal stage or in neonates and older. As previously mentioned, higher levels of HbF are associated with less severe sickle cell complications because HbF is known to have a protective effect. Molecular studies have induced HbF, which has reduced the clinical symptoms of SCD.³⁶ CRISPR/Cas9 could provide therapeutic results by increasing levels of HbF by reactivating the gene in patients at early or later stages of life.

Two studies have been done with CRISPR/Cas9 to show that biologically, SCD can be cured. In one study, CRISPR/Cas9 has successfully edited out the sickle cell gene in human stem cells.³⁷ This study also used stem cells from patients with β thalassemia. Work done has been sufficiently successful for researchers to start preparing for US Food and Drug Administration approval of human trials.³⁸ In another study, CRISPR/Cas9 edited human hematopoietic stem/progenitor human cells to reduce the amount of sickled hemoglobin RNA produced for over 4 months at a level that showed that the treatment could have therapeutic benefits.³⁹ Additionally, reproducible protocols have demonstrated how to

²³Ibid.

²⁴Op. cit. note 20.

²⁵Walters, M. C., Storb, R., Patience, M., Leisenring, W., Taylor, T., Sanders, J. E., ... Sullivan, K. M. (2000). Impact of bone marrow transplantation for symptomatic sickle cell disease: An interim report. *Blood*, 95(6), 1918–1924.

²⁶Ibid.

²⁷Ibid.

²⁸Walters, M. C., Patience, M., Leisenring, W., Eckman, J. R., Scott, J. P., Mentzer, W. C., Davies, S. C., ... Sullivan, K. M. (1996). Bone marrow transplantation for sickle cell disease. *New England Journal of Medicine*, 335(6), 369–376.

²⁹Ibid.

³⁰Ibid.

³¹Hoban, M. D., Orkin, S. H., & Bauer, D. E. (2016). Genetic treatment of a molecular disorder: Gene therapy approaches to sickle cell disease. *Blood*, 127(6), 839–848; Zhang, H., & McCarty, N. (2016). CRISPR-Cas9 technology and its application in haematological disorders. *British Journal of Haematology*, 175(2), 208–225; Huang, X., Wang, Y., Yan, W., Smith, C., Ye, Z., Wang, J., Gao, Y., ... Cheng, L. (2015). Production of gene-corrected adult β -globin protein in human erythrocytes differentiated from patient iPSCs after genome editing of the sickle point mutation. *Stem Cells*, 33(5), 1470–1479.

³²Bunn, H. F. (1997). Pathogenesis and treatment of sickle cell disease. *New England Journal of Medicine*, 337(11), 762–769.

³³Huang, et al., op. cit. note 31; Smith, C., Abalde-Atristain, L., He, C., Brodsky, B. R., Braunstein, E. M., Chaudhari, P., ... Ye, Z. (2015). Efficient and allele-specific genome editing of disease loci in human iPSCs. *Molecular Therapy*, 23(3), 570–577; Loucari, C. C., Patsali P., van Dijk, T. B., Stephanou, C., Papisavva, P., Zanti, M., ... Kleanthous, M. (2018). Rapid and sensitive assessment of globin chains for gene and cell therapy of hemoglobinopathies. *Human Gene Therapy Methods*, 29(1), 60–74; Antoniani, C., Meneghini, V., Lattanzi, A., Felix, T., Romano, O., Magrin, E., ... Miccio, A. (2018). Induction of fetal hemoglobin synthesis by CRISPR/Cas9-mediated editing of the human β -globin locus. *Blood*, 131(17), 1960–1973; Park, S., Gianotti-Sommer, A., Molina-Estevéz, F. J., Vanuytsel, K., Skvir, N., Leung, A., ... Murphy, G. J. (2017) A comprehensive, ethnically diverse library of sickle cell disease-specific induced pluripotent stem cells. *Stem Cell Reports*, 8(4), 1076–1085.

³⁴Huang et al., op. cit. note 31.

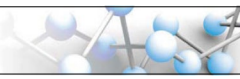
³⁵Dever, D., Bak, R. O., Reinisch, A., Camarena, J., Washington, G., Nicolas, C. E., ... Porteus, M. H. (2016). CRISPR/Cas9 β -globin gene targeting in human haematopoietic stem cells. *Nature*, 539(7629), 384–389.

³⁶Sankaran, V. G. & Orkin, S. H. (2013). The switch from fetal to adult hemoglobin. *Cold Spring Harbor Perspectives in Medicine*, 3(1). <https://doi.org/10.1101/cshperspect.a011643>.

³⁷Op. cit. note 35.

³⁸NIH, op. cit. note 4.

³⁹DeWitt, M. A., Magis, W., Bray, N. L., Wang, T., Berman, J. R., Urbinati, F., ... Corn, J. E. (2016). Selection-free genome editing of the sickle mutation in human adult hematopoietic stem/progenitor cells. *Science Translational Medicine*, 8(360), 1–9.



achieve genetic mutations in human hematopoietic stem cell transplantation-based therapies like those for SCD.⁴⁰ In other forms of anemia like Fanconi anemia, somatic cells taken from patients have successfully been reprogrammed to create patient-specific iPSCs.⁴¹ Taken together, previous research shows that the prospect of curing SCD using CRISPR/Cas9 warrants ethical discussions about why SCD should be included in CRISPR/Cas9 research.

2 | THE CASE IN FAVOR OF INCLUDING SCD IN CRISPR/CAS9 RESEARCH

Although a strong biological case has been made for applying CRISPR/Cas9 to edit the sickle cell single-gene mutation, the ethical benefits of including SCD in CRISPR/Cas9 research require more attention.⁴² A strong case in favor of including SCD in CRISPR/Cas9 research can be made. The ethical case is rooted in beneficence and justice which seeks to improve health and remedy the historical and sociopolitical injustices in research and care for patients with SCD. The benefits of including SCD in CRISPR/Cas9 clinical trials are distributive justice in research, reparative justice for patients with SCD in the health-care system, and benefit-sharing in a research and clinical setting.

2.1 | Distributive justice in research

A key argument in the case in favor of including SCD in CRISPR/Cas9 research, the benefit of distributive justice in research is that thus far, attempts to treat and cure SCD point to a history of neglect. This neglect emerges from the delays to recognize the severity of SCD nationally, insufficient epidemiological data, and insufficient therapeutic and curative research.

The neglect of SCD in research settings was nationally acknowledged in the USA in the early 1970s by President Richard Nixon, who said, "It is a sad and shameful fact that the causes of this disease have been largely neglected throughout our history. We cannot rewrite this record of neglect, but we can reverse it."⁴³ To reverse this neglect, President Nixon signed into law the National Sickle Cell Anemia Control Act of 16 May 1972 and called for increased research funding for the disease.⁴⁴ With this speech and Act, President Nixon voiced and brought to light what those affected with SCD already knew—that individuals with SCD faced double injury by being part of a socially, politically,

and economically marginalized race as well as carrying the burden of the disease.

Injustice also emerges in the collection of epidemiological data. In comparison to other diseases, communicable and non-communicable, there are imprecise data on the prevalence, incidence, and mortality of SCD nationally and globally.⁴⁵ Those who suffer from the illness are not accurately represented because of this lack of data. The lack of data is significantly worse in developing countries where children with SCD often die young without ever being formally diagnosed or treated.⁴⁶ This is especially detrimental as the burden of the disease is higher in these countries. Furthermore, imprecise data do not allow for research-based medicine to be conducted properly.

In addition to the lack of epidemiological data, insufficient empirical data about preventative and curative efforts in the USA and globally have perpetuated the high morbidity and mortality of SCD. One of the main steps to prevent increased childhood mortality is genetic testing at birth. Early testing of children improves the outcomes for those diagnosed with SCD, especially the under-5-year-old mortality rates.⁴⁷ After prophylactic penicillin was proved to reduce the incidence of pneumococcal sepsis, the National Institutes of Health (NIH) recommended in 1987 that all newborns be tested for SCD.⁴⁸ However, it was not until 2006 that all 50 states implemented this recommendation.⁴⁹ Globally, many ministries of health with populations severely affected by SCD have still not begun to see the burden of the disease as a serious public health issue.⁵⁰ Those who are diagnosed with SCD are given hydroxyurea, prophylactic penicillin to the age of 5 years, and blood transfusions as therapeutic treatments.⁵¹ However, the NHLBI Evidence-Based Management of Sickle Cell Disease Report of 2014 notes that good quality research data and high-quality evidence is still needed as all areas of SCD management are still waiting emergent information.⁵²

The evidence-based research that the NHLBI advocates is being supported by the NIH's financial investment of almost one billion dollars for SCD since the time President Nixon acknowledged that there was a lack of effort to prevent, treat, and cure SCD. Despite this financial investment, the estimated allocation amount of 107 million dollars for 2019 is lower than the 115 million dollars allocated

⁴⁰Bak et al., op. cit. note 1.

⁴¹Zhang and McCarty. Op. cit. note 31; Raya, A., Rodríguez-Pizà, I., Guenechea, G., Vassena, R., Navarro, S., Barrero, M. J., ... Izpisua Belmonte, J. C. (2009). Disease-corrected haematopoietic progenitors from fanconi anaemia induced pluripotent stem cells. *Nature*, 460(7251), 53–59.

⁴²Rodríguez, E. (2016). Ethical issues in genome editing using Crispr/Cas9 system. *Journal of Clinical Research & Bioethics*, 7(2), 1–4.

⁴³Wailoo, K. (2017). Sickle cell disease—a history of progress and peril. *New England Journal of Medicine*, 376(9), 805–807.

⁴⁴Ibid.

⁴⁵Chakravorty S. & Williams, T. N. (2014). Sickle cell disease: A Neglected chronic disease of increasing global health importance. *Archives of Disease in Childhood*, 100(1), 48–53.

⁴⁶Grosse, S. D., Odame, I., Atrash, H. K., Amendah, D. D., Piel, F. B., & Williams T. N. (2011). Sickle cell disease in Africa: A neglected cause of early childhood mortality. *American Journal of Preventive Medicine*; 41(6), 398–405.

⁴⁷Ibid.

⁴⁸Lane, P. (2001). *Newborn screening for hemoglobin disorders. Information for sickle cell and thalassemia disorders*. Denver, CO: University of Colorado Health Sciences Center. Retrieved from <http://sickle.bwh.harvard.edu/screening.html>; NIH Consensus Development Conference. (1987). Newborn screening for sickle cell disease and other hemoglobinopathies. *JAMA*, 258(9), 1205–1209.

⁴⁹Benson J. M. & Therrell, B. L. (2010). History and current status of newborn screening for hemoglobinopathies. *Seminars in Perinatology* 34(2), 134–144.

⁵⁰Op. cit. note 46.

⁵¹Op. cit. note 22.

⁵²Ibid.

in 2018.⁵³ While this funding will help to make strides in treating SCD, the use of CRISPR/Cas9 shows patients with SCD that the outdated treatments for symptoms are not enough and that precarious bone marrow transplants are not the only curative option. The clinical research industry has the opportunity to make a strong statement to patients with SCD that it is invested not only in finding ways to treat symptoms but, explicitly, in using funding and cutting-edge biotechnology to cure the disease.

2.2 | Reparative justice in the health-care system

Patients with SCD are deeply engaged with the health-care system and often have several different health-care providers whom they see regularly to manage symptoms. Despite their intimate relationship with the health-care system, patients do not always feel that they belong there or that they are treated with the respect and dignity they deserve. While blacks in the USA have historically distrusted the health-care system and research industry, this atmosphere is changing and trust between these parties is increasing.⁵⁴ Including patients in groundbreaking CRISPR/Cas9 research could continue to improve the precarious patient-provider relationship by signaling to patients with SCD that the clinical setting is engaged in improving their care through research. As previously mentioned, the use of CRISPR/Cas9 would signal to patients that while their providers are invested in treating their symptoms, they are also invested in curing the disease.

Patients with SCD are often considered pariahs and under-medicated or completely denied pain medication when they come into emergency rooms with sickle cell crises.⁵⁵ The major question is whether patients with SCD are treated with mistrust because of their race. In comparison with their white counterparts, blacks' pain is often undertreated, and black patients are humiliated through drug panels or leave in pain.⁵⁶ This erodes the patient-provider relationship and obstructs communication that could help prevent or treat issues that patients are having. The need to continue to repair the patient-provider relationship also shows up in genetic counseling sessions. In some genetic counseling conversations, SCT parents were reminded of racial genocide beliefs similar to those about the creation of the HIV/AIDS outbreak.⁵⁷

Conversations meant to educate parents on SCD were perceived to be antagonistic and suspicious.⁵⁸ Given the historical lack of trust amongst those most affected by SCD—black—people—further distrust and miscommunication is detrimental to improving health.⁵⁹

In order to moderate the negative feelings that patients with SCD may have towards providers, providers should understand the historical context of why patients with SCD may mistrust health-care providers. If health-care providers have historically sensitive conversations with their patients with SCD about CRISPR/Cas9 research, greater trust could be built between them and their patients. By incorporating good research practices while discussing emerging research and the possible curative efforts of CRISPR/Cas9, health-care providers will signal to their patients that they are interested in understanding how SCD could benefit from innovative biotechnology. These conversations would make it more visible to patients with SCD that many different actors understand that more needs to be done to treat and cure their illness. This requires clinicians and researchers working together to bring work done at the research bench to the bedside.⁶⁰

2.3 | Benefit-sharing

Benefit-sharing is connected to the principle of distributive justice and ensures that there is an ethical and fair distribution of new biotechnologies. In the field of genomic biotechnology, the Human Genome Organization committee on Ethics, Law, and Society has defined benefits as 'good(s) that contribute to the well-being of an individual and/or a given community' which 'transcend avoidance of harm (non-maleficence) in so far as they promote the welfare of an individual and/or of a community'.⁶¹ Benefit-sharing requires that benefits from research impact not only those who participate in research.⁶²

In the case of SCD, benefit-sharing would ensure that not only those who directly participate in research gain the curative benefits if CRISPR/Cas9 proves to be a successful curative approach for SCD. The larger population of SCD sufferers, whether in the States or abroad, should stand to gain. Benefit-sharing would also ensure that benefits in the clinical setting are shared by patients who do not directly participate in research. For example, clinical providers who have no direct relationship with CRISPR/Cas9 clinical trial patients should still have conversations with their patients about CRISPR/Cas9 research. In doing so, other patients would have the benefit of feeling included in clinical research and feeling that the gravity of their illness is acknowledged by the clinical and research community. An additional benefit is the financial affordability and accessibility of CRISPR/Cas9. This benefit is particularly important because the financial costs of

⁵³NHLBI. (2012). *Sickle cell disease research & care*. Bethesda, MD: NIH. Retrieved from <https://www.nhlbi.nih.gov/news/2012/sickle-cell-disease-research-care>; NIH. (2018). *Estimates of funding for various research, condition, and disease categories (RCDC)*. Bethesda, MD: NIH. Retrieved from https://report.nih.gov/categorical_spending.aspx.

⁵⁴Boulware L. E., Cooper L. A., Ratner, L. E., LaVeist, T. A., Powe, N. R. (2003). Race and trust in the health care system. *Public Health Reports*, 118(4), 358–365.

⁵⁵Zemsky, W. T. (2010). Evaluation and treatment of sickle cell pain in the emergency department: Paths to a better future. *Clinical Pediatric Emergency Medicine*, 11(4), 265–273.

⁵⁶Campbell, C. M., & Edwards, R. R. (2013). Ethnic differences in pain and pain management. *Pain Management*, 2(3), 219–230; Op. cit. note 43.

⁵⁷Westergaard, R. P., Beach, M. C., Saha, S., & Jacobs, E. A. (2014). Racial/ethnic differences in trust in health care: HIV conspiracy beliefs and vaccine research participation. *Journal of General Internal Medicine*, 29(1), 140–146; Ross, M. W., Essien, E. J., & Torres I. (2006). Conspiracy beliefs about the origin of HIV/AIDS in four racial/ethnic groups. *Journal of Acquired Immune Deficiency Syndromes*, 41(3), 42–344.

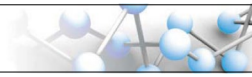
⁵⁸Op. cit. note 43.

⁵⁹Kennedy, B. R., Mathis, C. C., & Woods, A. K. (2007). African Americans and their distrust of the health care system: Healthcare for diverse populations. *Journal of Cultural Diversity*, 14(2), 56–60.

⁶⁰NIH, op. cit. note 19, p. 94.

⁶¹HUGO Ethics Committee. (2000). Hugo Ethics Committee statement on benefit sharing. *Clinical Genetics*, 58: 364–366, p. 3.

⁶²Ibid.; Lee, S. S. J. (2003). Race, distributive justice and the promise of pharmacogenomics. *American Journal of Pharmacogenomics*, 3(6), 385–392.



SCD are so high. Access to health care for those with SCD is often met by financial boundaries due to the extensive care that patients require. One study showed that patients with SCD spent, on average, \$1,389 a month and \$460,151 over a lifetime on health care.⁶³ For patients with SCD whose care is unmanaged properly, unexpected hospitalizations may cost them as much as \$7,637.⁶⁴ If CRISPR/Cas9 is expensive, adequate benefit-sharing would encourage measures to reduce financial barriers for SCD patients.⁶⁵ If CRISPR/Cas9 treatment costs are low, then access to care becomes cheaper for patients with SCD who already have significant financial health-care burdens.

If CRISPR/Cas9 is affordable, governmental health-care spending would also decrease. Presently, governmental health-care spending for patients with SCD through Medicare and Medicaid is extremely high as many patients with SCD are on Medicare and Medicaid. In 2004, almost \$500 million was spent on treating SCD.⁶⁶ Preventing hospitalizations through improved access to health care and using CRISPR/Cas9 to fix the single-point mutation has the potential to lower costs for individuals and the entire health-care system.

3 | THE CASE AGAINST INCLUDING SCD IN CRISPR/CAS9 RESEARCH

3.1 | CRISPR/Cas9 is a risky choice technology

Opponents of including SCD in CRISPR/Cas9 research will first argue that CRISPR/Cas9 is not refined enough to justify clinical trials. The opponents' argument should give pause, as CRISPR/Cas9 treatments are still being refined. While great strides have been made in gene therapy there are reasonable concerns about the type of gene therapy used, the safest method of delivery for CRISPR/CAS9, and gene therapy's efficacy.⁶⁷ Gene therapies are categorized as somatic or germline. Somatic gene therapies alter the individual's genes without passing the effects to the next generation. In contrast, germline gene therapies also alter the next generation. Somatic gene therapies are currently authorized in clinical trials in the USA whereas germline gene therapies are not actively studied in research with humans.⁶⁸ Future research must also find the safest and most efficacious method of delivery for CRISPR/CAS9 whether in vivo, in vitro, or ex vivo.⁶⁹

While they are used in clinical research, somatic gene therapies are not without risk and could give rise to issues of vector delivery, gene control, and targeting. Viruses are the most commonly used vector, given their evolutionary ability to deliver a therapy to a recipient. While viruses are efficient, problems such as toxicity and negatively impacting the immune system can arise. Additionally, work must be done to increase the specificity of CRISPR/Cas9 when deploying a virus because, once a part of the genome has been edited, it is permanently changed.⁷⁰ While off-target mutations are rare, the precariousness of gene control and targeting could give rise to accidental germline transfers or mosaicism.⁷¹

In 2015 Liang and colleagues successfully severed the β -globin gene in human embryos. However, the altered embryos had off-target mutations and were mosaic; that is, they contained several different types of alleles.⁷² A gene therapy study done by Ribeil and colleagues transplanted a non-sickling β -globin gene into a patient.⁷³ Fifteen months after the procedure, the biologic features of the disease and crises had stopped, and 50% of the anti-sickling β -globin cells were still present. While this study was successful, more insight into the efficacy and risk-benefit analysis of CRISPR/Cas9 for SCD will emerge when the results of human trials are analyzed.

As in cases of bone marrow transplants, part of determining the risk-benefit analysis is dependent on the severity of the participant's case and their willingness to participate. The foundation of conducting ethical research is having willing and informed participants who believe the researchers' claims that the benefits of the research outweigh the risks.⁷⁴ For many participants in curative trials, the severity of participants' symptoms justifies the more than minimal risk of bone marrow transplants. To be included in bone marrow transplant studies, participants had to have experienced a history of stroke, recurrent acute chest syndrome, or recurrent painful crises.⁷⁵ In the moments when the disease is becoming extremely burdensome,

⁶³Kauf, T. L., Coates, T. D., Huazhi, L., Mody-Patel, N., & Hartzema, A. G. (2009). The cost of health care for children and adults with sickle cell disease. *American Journal of Hematology*, 84(6), 323–327.

⁶⁴Singh, R., Jordan, R., & Hanlon, C. (2014). Economic impact of sickle cell hospitalization. *Blood*, 124(2), 5971.

⁶⁵Sherkow J. (2017). CRISPR, patents, and the public health. *Yale Journal of Biology and Medicine*, 90(4), 667–672.

⁶⁶Ibid.

⁶⁷Wirth, T., Parker, N., & Ylä-Herttua, S. (2013). History of gene therapy. *Gene*, 525(2), 162–169.

⁶⁸National Human Genome Research Institute. (2006). *Germline gene transfer*. Bethesda, MD. Retrieved from <https://www.genome.gov/10004764/germline-gene-transfer/>.

⁶⁹Zhang and McCarty. Op. cit., note 31.

⁷⁰Lin Y., Cradick, T. D., Brown, M. T., Deshmukh, H., Ranjan, P., Sarode, N., ... Bao, G. (2014). CRISPR/Cas9 systems have off-target activity with insertions or deletions between target DNA and guide RNA sequences. *Nucleic Acids Research*, 42(11), 7473–7485; P. Liang et al., op. cit. note 3; Cox, D. B. T., Platt, R. J., & Zhang, F. (2015). Therapeutic genome editing: prospects and challenges. *Nature Medicine*, 21(2), 121–131.

⁷¹Veres A., Gosis B. S., Ding, Q., Collins, R., Ragavendran, A., Brand, H., ... Musunuru K. (2014). Low incidence of off-target mutations in individual CRISPR-Cas9 and TALEN targeted human stem cell clones detected by whole-genome sequencing. *Cell Stem Cell*, 15(1), 27–30; Cox et al., op. cit. note 70; National Academies of Science Engineering Medicine. (2018). *Human genome editing initiative*. Washington, DC: National Academies of Science Engineering Medicine. Retrieved from <http://nationalacademies.org/gene-editing/index.htm>; National Academies of Science Engineering Medicine. (2018). *International summit on human gene editing: A global discussion*. Washington, DC: National Academies of Science Engineering Medicine. Retrieved from <https://www.nap.edu/read/21913/chapter/1>; Nuffield Council on Bioethics. (2016). *Genome editing: An ethical review*. London: Nuffield Council on Bioethics. Retrieved from <http://nuffieldbioethics.org/wp-content/uploads/Genome-editing-an-ethical-review.pdf>.

⁷²Liang et al., op. cit. note 3.

⁷³Ribeil, J. A., Hacein-Bey-Abina, S., Payen, E., Magnani, A., Semeraro, M., Magrin, E. P., ... Cavazzana M. et al. (2017). Gene therapy in a patient with sickle cell disease. *New England Journal of Medicine*, 376(9), 848–855.

⁷⁴U.S. Department of Health & Human Services. Office for Human Research Protections. 1979. *The Belmont report*. Rockville, MD: Office for Human Research Protections. Retrieved from <https://www.hhs.gov/ohrp/regulations-and-policy/belmont-report/read-the-belmont-report/index.html#>.

⁷⁵Op. cit. note 28, pp. 369–376.

patients with SCD are still able to exercise their autonomy and choose bone marrow transplants.

In research that has been and could be conducted on patients with SCD, the principle that should be invoked is “nothing about us, without us”.⁷⁶ This phrase is often used in disability communities to articulate the view that research, campaigns, and policies meant to benefit a specific group of people cannot be run without the input of members of the specific community.⁷⁷ The benefit of including patients with SCD in CRISPR/Cas9 trials is that they can assert when the disease's severity warrants the risk of CRISPR/Cas9 clinical research trials. In doing so, patients with SCD have the dignity to engage in their health-care decisions.

3.2 | A lack of participation

Opponents argue that SCD should not be included in CRISPR/Cas9 research because there will be no willing participants. They argue this based on the history of negative research with blacks in the USA. These opponents cite the memory of the Tuskegee syphilis study as a reason why distrust is perpetuated.⁷⁸ They also argue that the distrustful relationship between blacks and the health-care system will prevent an uptake in research participants. Despite this negative history, blacks and health-care professionals are currently at a stage where there is an upward trend towards trust.⁷⁹

Opponents argue that patients will feel as if they are being used in research studies to only benefit white patients. While this argument follows from the history of the Tuskegee syphilis study, the purpose of CRISPR/Cas9 studies would be to focus on curing SCD.⁸⁰ It would be up to researchers to describe clearly the purpose of the study during the informed consent process. Additionally, despite having extensive knowledge of the Tuskegee syphilis study, blacks are still likely to participate in clinical research—especially compared with their white counterparts who have knowledge of the Tuskegee study.⁸¹

Despite the history of research injustice in America, patients with SCD say that they are open to clinical research opportunities. However, they make it clear that researchers must find new and innovative ways to recruit participants while focusing on building trust.⁸² When these changes and larger institutional changes are heeded and implemented, they increase the participation of blacks and other racial minorities in clinical trials.⁸³ Additionally, patients

with SCD say that there needs to be a larger focus on educating patients about the potential benefits of the research.⁸⁴ All these suggestions are at the crux of the informed consent process and good research practices. According to the rules and regulations laid out in the *Belmont Report*, in order to have consenting and competent individuals researchers must be able to present the risks and benefits of a study in a way that is clearly accessible to and understood by participants.⁸⁵ Focusing attention on improving recruitment through the informed consent process can increase participation in clinical trials.

Including SCD in CRISPR/Cas9 research studies would increase opportunities for patients with SCD to learn about research being conducted to try to cure SCD. Other forms of research should include the best messaging techniques to reach patients with SCD and quality improvement activities in the clinical setting. As suggested by patients with SCD who have participated in research studies, researchers should be transparent that participating in a study may benefit the individual or the larger sickle cell community.⁸⁶ With this transparency, researchers may more easily find willing participants and continue to increase the participation of blacks in clinical research.⁸⁷

3.3 | The burden of SCD is low

Opponents will also make the claim that the burden of SCD, defined in terms of frequency, financial costs, and years of life lost, is not high enough to necessitate the allocation of CRISPR/Cas9 resources. This argument is easily refuted as SCD is the “most common inherited blood disorder in the United States.”⁸⁸ Furthermore, the frequency of SCD is extremely high globally. Countries in West and Central Africa like Ghana, Gabon, Nigeria, Cameroon, and the Republic of Congo have sickle cell trait prevalence levels as high as 20 and 30%.⁸⁹ Uganda has one of the highest trait prevalence rates at 45%.⁹⁰ In some countries, about 2% of the population has the disease where the trait prevalence is above 20%.⁹¹ However, access to health clinics and the adequate standard of care for SCD—prophylactic penicillin and folic acid—is minimal, if it exists at all.⁹² Additionally, the ministries of health in these countries do not consider SCD a top priority.⁹³ The impact of CRISPR/Cas9 would be global in reach and prevent the burden of disease for nations that

⁷⁶ Charlton, J. I. (2000). *Nothing about us without us: Disability, oppression and empowerment*. Berkeley, CA: University of California Press.

⁷⁷ Ibid.

⁷⁸ Katz, R., Kegeles, S. S., Kressin, N. R., Green, B. L., James, S. A., Wang, M. Q., ... Claudio, C. (2008). Awareness of the Tuskegee syphilis study and the US Presidential apology and their influence on minority participation in biomedical research. *American Journal of Public Health, 98*(6), 1137–1142.

⁷⁹ Op. cit. note 54.

⁸⁰ Op. cit. note 78.

⁸¹ Ibid.

⁸² NHLBI. (2017). For diversity in clinical trials, “include us!”, patients say. Bethesda, MD: NIH NHLBI. Retrieved from <https://www.nhlbi.nih.gov/news/2017/diversity-clinical-trials-include-us-patients-say>.

⁸³ Anwuri, V.V., Hall, L.E., Mathews, K., Springer, B.C., Tappenden, J. R., Farria, D. M., ... Colditz G.A. (2013). An institutional strategy to increase minority recruitment to therapeutic trials. *Cancer Causes & Control, 24*(10), 1797–1809.

⁸⁴ Op. cit. note 82.

⁸⁵ Op. cit. note 74.

⁸⁶ Op. cit. note 82.

⁸⁷ Ibid.

⁸⁸ NIH, U.S. National Library of Medicine, op. cit. note 6, p. 1.

⁸⁹ Regional Committee for Africa. (2006). Sickle-cell disease in the African region: Current situation and the way forward. Addis Ababa: WHO. Retrieved from <https://www.afro.who.int/sites/default/files/2017-06/AFR-RC56-17%20Sickle%20Cell%20Disease%20-%20Final.pdf>.

⁹⁰ Ibid.

⁹¹ Ibid.

⁹² Mulumba, L. L., & Wilson, L. (2015). Sickle cell disease among children in Africa: An integrative literature review and global recommendations. *International Journal of Africa Nursing Sciences 3*, pp. 56–64.

⁹³ Op. cit. note 46.

currently struggle to provide adequate support for disease sufferers. The high burden of disease is also clearly visible in the aforementioned high costs of SCD management for individuals and the government in the USA.⁹⁴ Furthermore, SCD individuals face significant years of life lost in comparison to their healthy counterparts.⁹⁵ Taken together, the high frequency of SCD, the high cost of care, and significant early mortality counters claims that the burden of SCD does not warrant inclusion in cutting-edge biotechnology research.

4 | CONCLUSION

Innovative genetic biotechnologies like CRISPR/Cas9 are rapidly creating the possibility of curing illnesses like SCD and improving the health of those affected. As the field of genetic biotechnology continues to develop, it is important to understand the ethical implications of biotechnology like CRISPR/Cas9. This article anticipates the eventual clinical delivery of CRISPR/Cas9 to lay out several ethical arguments that supplement the biological arguments for including SCD in CRISPR/Cas9 research. The first benefit is achieving distributive justice in research. The second is continuing to repair the distrustful relationship between the health-care system and SCD patients. The third is benefit-sharing for all those affected with SCD who do not participate directly in CRISPR/Cas9 research.

Opponents of including SCD in CRISPR/Cas9 research argue three arguments. They argue that SCD is a risky choice for research, that researchers will not find participants for studies, and that the burden of SCD is low. Of these arguments, the first gives pause while the other two are easily refuted. On balance, the arguments for including SCD in innovative CRISPR/Cas9 research are greater than

the arguments against it. As CRISPR/Cas9 biotechnology develops to become feasible for human delivery, it is pertinent to consider the ethical advantages of including SCD in clinical research trials.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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⁹⁴Op. cit. note 64.

⁹⁵NHLBI, op. cit. note 19.