

Published in final edited form as:

Lancet. 2017 June 17; 389(10087): 2355–2358. doi:10.1016/S0140-6736(17)31615-X.

Sickle cell disease: tipping the balance of genomic research to catalyse discoveries in Africa

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The completion of the Human Genome Project and the use of CRISPR/Cas9 for gene editing have begun to transform the diagnosis and management of disease. Sickle cell disease has been considered a perfect model for genomic research because it is a monogenic disease that is common and causes substantial morbidity and mortality but has no cure. The recent use of gene editing to modify disease severity¹ and a case report of a patient with sickle cell disease who received successful treatment with gene therapy² highlight the potential for translating genome-based knowledge into health benefits. But will these advances benefit patients in Africa³ where the burden is high? Sub-Saharan Africa has an estimated 64% of the 300 000 people born annually with sickle cell disease in the world, mortality is high, and few effective interventions have been introduced.^{4,5} World Sickle Cell Day on June 19, 2017, provides an opportunity to examine progress and persistent challenges in Africa.

In the past decade, the health community has recognised the public health importance of sickle cell disease⁶ and efforts are being made by African countries to introduce interventions such as newborn screening, infection prophylaxis, exchange blood transfusion,

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and hydroxyurea treatment that increase survival and improve quality of life.⁷ However, resource limitations in many African countries mean that these effective interventions have to be complemented by initiatives that strengthen health systems, ensure sustainable health financing, and improve policies that will provide universal health care for patients with sickle cell disease at primary, secondary, and tertiary level health facilities. The level of care is variable between African countries, as well as within a country, where the needs range from setting up haemopoietic stem cell transplantation in large urban hospitals to ensuring that children with the disease receive oral penicillin in small rural health facilities. While expanding such care to patients in Africa is vital, research capacity must also be strengthened since the spectrum of sickle cell disease in Africa differs from that in other countries.

Research in sickle cell disease in Europe, Jamaica, and the USA has helped unravel key aspects of the disease—eg, fetal haemoglobin as one of the strongest modifiers of disease severity, the effectiveness of hydroxyurea in reducing painful crises, and the prevention of cerebrovascular stroke with blood transfusion. However, fundamental knowledge gaps still exist—eg, understanding the precise mechanism of fetal to adult haemoglobin switching and identifying disease-modifier prediction models that would allow stratification of patients and enable interventions to be targeted to high-risk individuals. Studying large sickle cell disease populations with well described phenotypes will advance such knowledge and longitudinal cohort studies are a rigorous way to understand disease spectrum, modifiers, mechanisms, and outcomes. The high prevalence of sickle cell disease in Africa would facilitate large-scale cohort studies, leading to new evidence and interventions. Such cohort studies are emerging in some parts of the continent, empowering African scientists to investigate the complexity of a monogenic condition with a heterogeneous expression of disease severity.^{8–10} For sickle cell disease research to be successful, however, an integrated, multidisciplinary approach is required that encompasses clinical, public health, environmental, social, population-based, and basic science disciplines. Furthermore, North–South, South–South, and intra-African collaborations must be encouraged.

The [Human Heredity and Health in Africa \(H3Africa\)](#) Initiative was established by the US National Institutes of Health (NIH) and the Wellcome Trust to develop capacity in genomic research in Africa.¹¹ This initiative included the establishment of [H3ABioNet](#), a pan-African bioinformatics network to collect, manage, and analyse health and genetic data in Africa. H3ABioNet has 32 research groups from 15 African countries, and two partner institutions in the USA.¹² The network supports H3Africa researchers and is helping to develop bioinformatics capacity across Africa and encourage sickle cell disease research through the development of sickle cell disease ontology to standardise terms related to all aspects of the disease. These efforts contributed to the first genome-wide association study in sickle cell disease from Africa,¹³ which was done in collaboration with the Wellcome Trust Sanger Institute.

More recently, the NIH funded the establishment of the Sickle Pan-African Research Consortium (SPARCO) that will develop infrastructure for sickle cell disease research, health care, education, and training, initially in Tanzania, Ghana, and Nigeria, with coordination from the Muhimbili University of Health and Allied Sciences. A potential

limitation in fully harnessing the gains from these efforts is poor integration and coordination across various research and clinical sites in Africa. To address this need, a data coordinating centre has been established to support SPARCO activities. The Sickle Africa Data Coordinating Center (SADaCC) is also funded by the NIH and is based at the University of Cape Town, leveraging the experience and expertise of H3ABioNet. To ensure sustainability that extends beyond funding cycles, the Sickle Pan-African Network (SPAN) has been formed and currently involves 17 African countries but will eventually include all countries on the continent. In addition, the African Newborn Screening and Early Intervention Consortium has been established, in partnership with the American Society of Hematology, following the *State of Sickle Cell Disease: 2016 Report*.¹⁴ These initiatives should enable efforts in health and science to be led from Africa so as to develop locally effective, evidence-based solutions to reduce the disease burden in Africa.

A critical foundation for this research is a well trained workforce in Africa. Although much still needs to be done to improve training, there has been some progress. Successful postgraduate training in haematology exists in Tanzania in health and science.¹⁵ In terms of postgraduate education in science, technology, engineering, and mathematics, there has been the establishment of the [Nelson Mandela Institutes](#) and [African Centres of Excellence](#) with support from the World Bank, while the Wellcome Trust has funded research training through different schemes such as fellowships and programmes. But there is a dearth of experience and expertise in management and analysis of data, especially big data, in most African institutions that could negatively impact genomics research on sickle cell disease on the continent. H3ABioNet and the [African Institute for Mathematical Sciences](#) are addressing this gap. All these education and training initiatives complement existing educational programmes and effectively increase the quantity and quality of expertise in Africa in health and research in sickle cell disease. Additional efforts to strengthen genomic research are needed in Africa, such as the establishment of biorepositories for disease as part of H3Africa in Nigeria, South Africa, and Uganda, as well as setting up birth or population-level cohort studies in Africa similar to the Precision Medicine Initiative in the USA and the UK BioBank. Finally, linking of genomic research to existing public health services in Africa, such as neonatal health, immunisation, and transfusion services, would leverage existing platforms and explore opportunities that could lead to the development of [Precision Public Health in Africa](#).

Finding scientific and health-care solutions in Africa that are locally relevant but with global impact is crucial to reduce the substantial disease burden across the continent. The importance of advocacy, particularly involving partnerships with patients' groups, was evident in the response to the HIV pandemic. Our vision is to have effective local and global partnerships that will successfully advance biomedical science and translate this knowledge into major improvements for patients with sickle cell disease in Africa.

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Scientists generating phenotype data for genomic research in sickle cell disease at Muhimbili University of Health and Allied Sciences, Tanzania