

PERSPECTIVE

How sickle cell crisis stymied modern medicine for 100 years, whilst a solution was hidden in plain sight: A hypothesis

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Abstract

Reversible sickle cells (RSCs) can become irreversible sickle cells (ISCs) after repeated episodes of sickling. The RSCs can revert to their original flexible discoid shape when reoxygenated; however, repeated sickling can damage the cell membrane, making it impossible for the cells to return to their standard shape and resulting in ISCs. Home oxygen therapy during the critical first half-hour after the onset of a crisis restores RSCs. It prevents them from progressing to a critical mass of ISCs, where the sickle cell crisis becomes established and intractable. Developing a medication to prevent and stop a sickle cell crisis within the golden half hour has been very difficult. The efficacy of oxygen therapy in preventing and aborting a crisis in the golden half hour is very promising. When you stop the crisis, you prevent severe pain, emergency care, hospitalisation and multi-organ damage. It would reduce the complications, disability and mortality rates linked to this chronic condition.

Keywords: *sickle cell disease; sickle cell crisis; hypoxia; oxygen; golden half-hour*

Received: 17 December 2023; Revised: 23 December 2024; Accepted: 30 December 2024; Published: 11 August 2025

The sickle cell mutation can be traced back to at least 7,300 years. The first recorded cases of sickle cell disease (SCD) were in Egypt during the predynastic period (~ 3200 BCE), in the Persian Gulf during the Hellenistic period (2,130 years before present) and in Ghana in 1670 CE [1].

For thousands of years, SCD has been an inevitable sentence of recurrent excruciating pain crises, resulting in complications, severe disabilities and death. In the modern era, the mortality rate for adults with the disease has risen by 1% every year since 1979. The median age at death in 2005 was 42 years for females and 38 years for males [2]. The dreaded feature of the disease is the sickle cell crisis. Developing a medication to stop a sickle cell crisis has proven difficult. On September 25, 2024, Pfizer withdrew Oxbryta (Voxelotor) from the market as patients on Oxbryta had more sickle cell crises than those on placebo [3]. Crizanlizumab-tmca (Adakveo), developed by Novartis, was approved by the United States Food and Drug Administration (US FDA) in November 2019 for reducing the frequency of sickle cell crises. In May 2023, the European Medicines Agency's (EMA's) Committee for Medicinal Products for Human Use (CHMP) revoked Novartis' approval for Adakveo [4] because Adakveo could not reduce the number of painful crises. We need to evaluate home oxygen therapy to prevent and stop the early stages of a sickle cell crisis.

Irreversible sickle cell (ISC) formation is time-dependent, and Hemoglobin S (HbS) sickling is reversible with reoxygenation [5]. In our clinical experience, this occurs within the first golden half hour (30 mins). When time progresses, the cells become irreversibly sickled. ISCs are circulating blood cells in patients with SCD that retain a sickled shape even when oxygenated [6]. In these irreversibly sickled cells, the structure of the cytoskeleton network is permanently altered. These are the cells that obstruct blood flow, cause severe pain and suffering and lead to multi-organ damage. By the time many of these patients seek medical care or arrive in the hospital, they are already experiencing irreversible sickling, which can no longer be reversed by oxygenation [7]. These cells remain until they are removed by destruction (haemolysis), phagocytosis or sequestration when an excessive amount of blood becomes trapped in the spleen, causing a dangerous drop in circulating blood volume (a decrease in haemoglobin of 2 g/dL) accompanied by enlargement of the spleen (splenomegaly). Clearing these sickled cells is a process that can take several weeks and results in a prolonged sickle cell crisis with complications, multi-organ damage and increased risk of death [8].

History

SCD was first described by Herrick in 1910 [9], when he observed a dental student who presented with pulmonary

symptoms. He further explained the ‘peculiar sickle-cell shape’ of the patient’s red blood cells. In 1927, Hahn and Gillespie [10] proposed that hypoxia caused the sickling of red blood cells by saturating a cell suspension with carbon dioxide, which induced shape changes. The level and effect of hypoxia in the causation of sickle cell pain crisis depend on the degree of anaemia, sedation, nocturnal hypoventilation as well as the presence of other triggers such as stress [11], exertion/exhaustion, alcohol ingestion, altitude, infection and cold, all of which can vary at any point in time [12, 13].

In a low-oxygen environment, sickle haemoglobin forms a sticky gel, characterised by a network of closely packed, parallel, rod-like structures, a process known as polymerisation. With polymerisation, the sickle haemoglobin cells become more rigid and change their shape to a sickle shape. The red blood cells are trapped and easily destroyed during their passage through the blood vessels and capillaries, resulting in anaemia and a complex cascade of processes that include inflammation and, ultimately, blood vessel occlusion (obstruction of blood vessels in almost every organ) with interruption of the blood supply and excruciating pain [13].

In 1930, Scriver and Waugh in Canada reported a case of sickle cell anaemia, wherein the number of sickle cells in the blood may be varied by the change of the partial oxygen (O₂) pressure; that this is a reversible reaction; and that sickling takes place when the O₂ pressure falls below 45 mm Hg [14]. In 1983, an article by Franck and Chiu [15] stated as follows:

Abnormalities in the availability of the phospholipids to exogenous probes have also been shown to occur in sickled erythrocytes. The accessibility of both aminophospholipids for chemical as well as enzymatic probes appears to be increased, not only in irreversibly sickled cells, but also in deoxygenated reversible sickle cells (RSCs), when compared to both normal cells or oxygenated (discoid) RSCs. Furthermore, it is of interest that RSCs not only possess the ability to readopt their discoid shape upon reoxygenation, but that this process also, for the greater part, restores the degree of accessibility of the glycerophospholipids to exogenous probes to the levels found in normal erythrocytes.

In 1991, another article by Robert Hebbel stated [5].

More precisely, sickling results in elevated translocation rates for added Phosphatidylcholine (PC) or lysoPC. For reversibly sickled cells, this destabilisation is reversible, with reoxygenation allowing a return to normal PC, translocation rates, and near-normal phosphatidylserine (PS) availability to phospholipase.

In a clinical trial by Zipursky et al. in August 1992, the effect of oxygen therapy on the number of ISC and RSCs

(reversible sickled cells) was studied in patients with sickle cell anaemia [7]. Inhalation of 50% oxygen in patients who were not in crisis resulted in a significant decrease in RSCs and a lesser decrease in ISCs. Inhalation of 50% oxygen in patients experiencing a crisis showed a substantial reduction in RSCs but not in ISCs. In the group of patients who received air (no supplemental oxygen), there was no significant change in RSCs or ISCs. In patients who were in a crisis, despite the reduction in RSCs in the oxygen-treated group, there was no significant difference between the air and oxygen groups in the duration of severe pain, opioid administration and hospitalisation. As mentioned previously, oxygen therapy when a sickle cell crisis is already established does not affect the population of ISC, as those cells must be cleared by haemolysis, phagocytosis or sequestration. RSCs can become ISCs after repeated episodes of sickling. During sickling, red blood cells become rigid and assume a sickle-shaped form, obstructing blood flow to the organs. The RSCs can revert to their original flexible discoid shape when reoxygenated; however, repeated sickling can damage the cell membrane, making it impossible for the cells to return to their standard shape and become ISCs [7]. Thus, oxygen therapy in the golden half hour after onset of a crisis restores RSCs and prevents them from progressing to a critical mass of ISCs, wherein the sickle cell crisis becomes established and intractable.

This means that if we can reverse the low-oxygen environment by providing home inhalation oxygen within the first golden half hour of a sickle cell crisis, we may be able to prevent the crisis from escalating. We have observed this effect in several sickle cell patients treated in our practice and many others now implementing home oxygen, provided there are no other triggers, such as colds and infections, involved.

By the time sickle cell patients seek medical care or arrive in the hospital, they are likely already experiencing irreversible sickling, which cannot be reversed by oxygenation. Based upon our clinical experience, the time-dependent golden half hour intervention for a sickle cell crisis, which can damage multiple organs, is like that of the golden hour for stroke when there is the best chance of restoring blood flow and saving brain tissue or that for myocardial infarction, wherein timely intervention impacts a patient’s survival and quality of life following a heart attack.

Discussion

In our practice, we have been able to reduce the incidence of sickle cell crisis as well as reduce hospitalisations by 90% in seven patients. This is of immense significance. The sickle cell crisis results in obstruction of blood flow, severe pain and suffering, and damage to organs. It results in severe life-threatening and disabling

complications, including acute chest syndrome, avascular necrosis of the hips (death of bone tissue due to lack of blood supply) with bone destruction, stroke, brain damage, priapism and kidney damage that may result in dialysis and increased risk of death. Thus, the key to preventing the disease is stopping the crisis at the first sign of it.

Now, we know that a low-oxygen environment causes a crisis, and reoxygenation within several minutes of the crisis may reverse most of the sickling. The next question will be when and where the majority of crises occur. Research as well as clinical history has already provided us with the answer. In a study of 21 screened participants, nine (43%) had sufficient nocturnal hypoxaemia to warrant oxygen therapy (≥ 5 min at $\text{SpO}_2 \leq 88\%$) [12]. In our clinical experience, the majority of crises (90%) occur during sleep, either at bedtime or in the daytime. Patients with SCD are fearful of going to sleep because they never know if they will wake up in a crisis.

Life experience of patients reveals struggles at night, restlessness from sickle cell pain and weeping at morning break with anger and trepidation [16], and another patient's childhood recollection of fear of the night because of her expectation of sickle cell crises 'I thought there was something about the hours between 2 and 5 a.m. that was just dangerous' [17]. During sleep, people breathe less efficiently than when awake. They have shallow or slow breathing, which reduces oxygen intake, a condition known as nocturnal hypoventilation [18]. Unless it is very severe, people with normal haemoglobin do not suffer any harmful effects. However, people with sickle cell anaemia are at greater risk from the low-oxygen environment during sleep. Studies have linked nocturnal hypoventilation with sickle cell haemoglobin polymerisation and sickle cell pain crisis. In a study, the authors concluded that low nighttime oxygen saturation was significantly associated with a higher rate of painful crises in childhood [18].

A low-oxygen environment causes sickle cell crisis, and most of these occur during sleep [12]. We may be able to prevent it by having sickle cell patients sleep with oxygen. Low-oxygen environments are exacerbated by one or more triggers, such as increased anaemia, stress, exertion or exhaustion, infection, sedation, alcohol ingestion, altitude (above 2,000 ft), a cold environment or a feeling of being unwell. However, following this principle means that all patients will need to have home oxygen immediately available to them for use as needed. In the absence of triggers, patients with SCD do not need to sleep with oxygen; however, if a patient wakes up in a crisis, oxygen should be immediately available to them. We have found that administering oxygen within the golden half-hour of a crisis can abort the crisis because HbS sickling is reversible with reoxygenation in the early stages [5].

Providing sickle cell patients with the scientific basis for their nighttime crisis and the use of oxygen to prevent those crises give them control over their illness and significantly alleviate their anxiety and fear of waking up in pain.

Proof of concept

The disease burden of sickle cell anaemia has improved with the advent of medications like hydroxyurea and Voxelator. These medications target the availability of oxygen at the molecular level to the sickle haemoglobin. Hydroxyurea increases haemoglobin F (HbF) production in RBCs and decreases sickling of HbS [19]. HbF evolved to potentiate the transfer of oxygen (O_2) from a mother's blood to foetal tissues, a goal achieved by the higher Oxygen affinity of Hb F compared with adult Hb A. Oxbryta (Voxelator) increases the affinity of the sickle haemoglobin for oxygen, thereby inhibiting sickling, reducing the amount of haemolysis and increasing haemoglobin levels [20, 21]. Oxbryta taken orally (at 500 mg, three tablets once daily) can raise the haemoglobin level of a person with sickle cell anaemia by 2–3 g/L within just a few days and in some cases can return close to normal levels [20] – almost as fast as a blood transfusion, and without the possible complications. However, at that dose, if administered long-term, it raises the haemoglobin to a level that is too high, increasing blood viscosity, and in SCD, increasing the risk of a vaso-occlusive crisis. In the clinical trial, Oxbryta did not have a significant effect on reducing pain crises compared with the placebo [21].

The only exception in our current advances is the Novartis \$665 million drug, Crizanlizumab-tmca (Adakveo), a humanised monoclonal antibody against P-selectin, which inhibits the adhesion of sickle erythrocytes and leukocytes to the endothelium [22]. The FDA approved Crizanlizumab in November 2019 for reducing the frequency of vaso-occlusive crises. In May 2023, the EMA's CHMP revoked Novartis' approval for Adakveo [23] after concluding that the med's benefits did not outweigh the risks. The decision was based on the results [24] of the global phase III study STAND (NCT03814746) trial, in which the drug did not outperform placebo. Specifically, Adakveo (crizanlizumab) was unable to reduce the number of painful crises that led to a healthcare visit. Adakveo-treated patients saw an average of 2.5 painful crises resulting in a healthcare visit over their first year of treatment, whilst patients in the placebo group had an average of 2.3. Furthermore, the average number of crises requiring a home healthcare visit or treatment was 4.7 in the Adakveo group compared with 3.9 in the placebo group. On January 10th, 2024, the UK Medicines and Healthcare products Regulatory Agency (MHRA), based on the same Phase III STAND study, revoked a conditional marketing authorisation for Adakveo to treat SCD [25].

The failure of this multimillion-dollar drug was predictable because the drug failed to target the hypoxic (low oxygen) milieu, wherein Hgb polymerisation is initiated. Instead, the drug targets downstream of the subsequent inflammatory cascade, by which time Hgb polymerisation is irreversible [22].

Inhalational oxygen

Oxygen may be obtained from oxygen cylinders or, more conveniently and with less maintenance, from portable or home oxygen concentrators, some of which are priced as low as \$450.00. An oxygen concentrator is a device that intakes the surrounding air to produce an inspired oxygen concentration (FiO_2) of 24–28% at 1–2 litres per minute flow by nasal cannula [26, 27]. The concentrator, using battery or electrical power, takes in air, compresses the air and passes it over a sieve bed containing zeolite. The zeolite adsorbs the nitrogen from the air, and the remaining gas, which is mostly oxygen, is released through a plastic tube to reach a nasal cannula or mask. The nitrogen is desorbed from the zeolite under reduced pressure and is vented into the atmosphere. The oxygen should be provided by continuous flow with an oxygen purity of 93 % + - 3 % at all flow rates. Pulse dose concentrators do not provide sufficient oxygenation and should not be used. Avoid smoking or using any electrical objects, such as electric blankets or hair dryers, near an oxygen concentrator. Also, keep flammable materials away from the device.

Air travel and high altitudes

Air travel is a hidden danger for sickle cell patients. During and following commercial airline flights, patients with SCD are known to experience complications such as bone pain, splenic infarction [20, 28, 29], osteonecrosis (avascular necrosis) of the hip and, in some cases, prolonged crisis resulting in death. These complications have been linked to protracted oxygen desaturation at high altitudes, with oxygen saturations measured as low as 77%, instead of the normal of 95–100% [30]. Continuous flow oxygen supplementation should be prescribed to ameliorate the low-oxygen environment that occurs at high altitudes during airline flights, which results in considerable harm to sickle cell patients who continue to experience injury and death after such flights. Some airlines will provide compressed medical oxygen for flights, whilst others require the patient to bring an oxygen concentrator that is certified for flight, which is more onerous and cost-prohibitive for many patients, and mechanical devices can fail during flight or at the destination.

Treatment of a crisis

Time is of the essence to abort the crisis within the golden half hour before severe pain produces chest splinting [31]

as inadequate respiration leads to further hypoxic sickling and a prolonged crisis requiring hospitalisation. Consequently, home oxygen therapy, should become standard initial treatment by the patient, family or caregiver.

We have applied the principle described above to seven patients with sickle cell anaemia over the last 20 years who have come to our specialist pain clinic for pain control. All our patients experienced most of their crises at night, during flights or whilst visiting high-altitude places. These patients were prescribed an oxygen concentrator to use at home. They were advised to sleep with oxygen, 1.5–2 litres/min by nasal cannula, only when there are one or more triggers such as increased anaemia, stress, exertion/exhaustion, infection, increased sedation, alcohol ingestion, altitude (above 2,000 ft), infection, cold environment, a feeling of being unwell, etc. In the absence of triggers, they do not have to sleep with oxygen. All our patients were able to abort a crisis by administering oxygen at the first sign of the crisis. The only exceptions were when the crises occurred outside the home or were induced by infection or hypothermia. This intervention reduced the frequency of sickle cell crises and hospitalisations. The failures were when crises were induced by cold or infection. (See Fig 1)

Cure – bone marrow transplant and gene therapy

There are now several curative options for SCD. The essence of these cures is to reduce sickle haemoglobin and provide increased oxygen capacity of the replacement haemoglobin. Two therapies LYFGENIA™ (lovotibeglogene autotemcel) [32, 33], also known as lovo-cel, and CASGEVY (exagamglogene autotemcel) [34] have recently been approved.

Casgevvy and Lyfgenia cost \$2.2 million and \$3.1 million per patient, respectively, for a course of treatment, which can take up to a year. The therapies require several other procedures, including chemotherapy before the treatments, which involve removing blood cells from a patient and modifying the DNA before re-introducing them into the body. The United States government has stated that it will negotiate an ‘outcomes-based agreement’ with the companies, meaning the prices for treatments will be tied to whether the therapy improves health outcomes [35]. It is essential to highlight that these curative therapies do not reverse pre-existing end-organ complications.

Home oxygen and timely treatment are more likely to prevent end-organ complications even for patients who will subsequently undergo gene therapy. Costs and availability of these new therapies will limit their global application, even in high-income countries. Capacity is limited. Bluebird Bio, the company that makes Lyfgenia, estimates that it can treat 85–105 patients per year with the gene therapy. The process is complex and time-consuming,

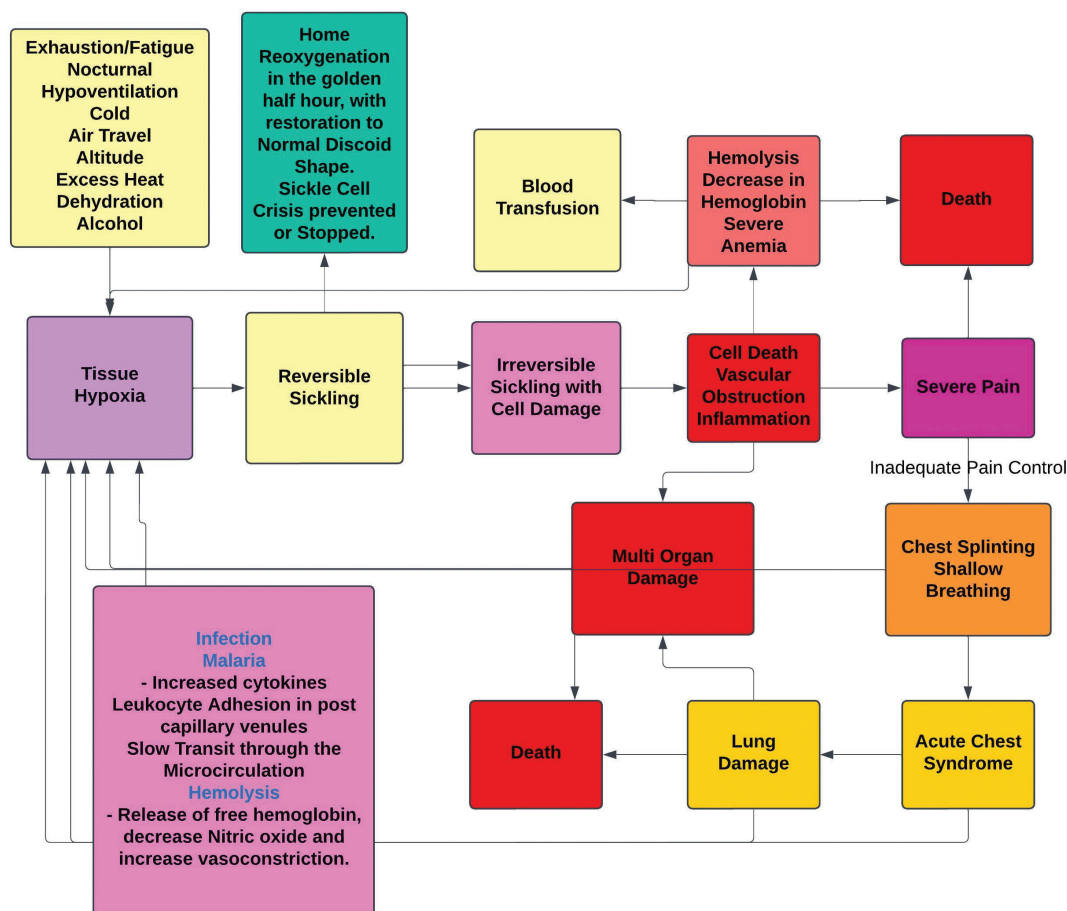


Fig. 1. Cascade of sickle cell crisis prevented by home oxygen.

and medical centres can only handle a limited number of patients because each person needs intensive care. Home oxygen will be the closest, most affordable and accessible alternative to gene therapy.

Conclusion

There is evidence that intervention with home inhalational oxygen can prevent and abort a sickle cell crisis promptly. The estimated global population of patients with SCD is 5.46–7.74 million people living with an SCD, with a mortality burden estimated at 376,000–467,000 in the year 2021 [36]. The mortality rate for adults with the disease has risen 1% every year since 1979 [2]. Half of adult sickle cell patients are dead by their early 40s [2]. The Healthcare Cost and Utilisation Project (HCUP) Statistical Brief presented statistics on inpatient stays amongst patients with SCD from 2000 through 2016 [37]. The number of hospital stays involving SCD for patients older than 45 years increased more than twice between 2000 and 2014. Over 70% of SCD-related stays had a principal SCD diagnosis. Nearly all stays for SCD and one-third of stays with a secondary diagnosis of SCD involved a pain crisis. Black patients accounted for 88.7%

of stays with a principal diagnosis of SCD (nearly all of which involved a pain crisis). Of the 134,000 stays involving SCD in 2016, 71.3% were specifically for SCD (i.e. SCD was the principal diagnosis). Nearly all stays with a principal diagnosis of SCD involved a pain crisis (96.0%). The leading reason for stays for patients with a secondary diagnosis of SCD was respiratory system-related illnesses, constituting 14.3% of those stays. Infectious and parasitic diseases and pregnancy were the second and third most common reasons for stays for patients with a secondary diagnosis of SCD, constituting 13.2 and 12.8%, respectively. In 2016, the aggregate cost of inpatient hospital stays for patients with a principal diagnosis of SCD was \$811.4 million. Amongst stays for SCD, the mean length of stay was around 5 days for adults and was approximately 1 day shorter for children [37]. SCD imposes a recognised economic burden on the US Healthcare system and society, primarily owing to inpatient hospitalisations and impaired quality of life. SCD causes \$1.5 billion in lost wages and productivity each year in the U.S. alone, according to the first study of its kind. That comes to more than \$650,000 lost over the average working life of a person living with the painful genetic disorder [38, 39].

The provision of inhalational oxygen can be implemented, but the initial outlay and ongoing costs are expensive. The cost of an in-home oxygen concentrator, with an average device use duration of 32.4 ± 30.7 months [40] and longer with proper maintenance, is often less than the cost of one hospital admission. The cost of an oxygen cylinder in the United States varies; one supplier charges \$234.00 with a refill cost of \$14.30 [41].

In Nigeria, the cost of an oxygen cylinder averages \$100.00, with a refill cost of \$15.00. That should last an average of 2–4 months, depending on usage, and a refill will be about \$1.00 per week. Suppose all patients with SCD require home oxygen, the initial cost will be \$0.60–\$1.46 billion, with refill costs between \$85 and \$90 million every 2–4 months, approximately \$340–\$350 per patient per year, in a country where the annual average family income is less than that \$1,200. In 2021, 515,000 babies were born with SCD globally [36], and this needs to be factored into yearly costs. Furthermore, 75% of all sickle cell patients live in sub-Saharan Africa, with Nigeria being the most endemic country in the world [42].

For such a low cost, if proven in a large-scale study, home inhalational oxygen will significantly reduce the burden of illness, disability and death in patients with SCD. The addition of inhalational oxygen will change lives for both patients and their families. Studies have shown that there are no deleterious effects from long-term use of oxygen [43]. There is good evidence from the literature that reoxygenation with inhalational oxygen at the early stages of a sickle cell crisis is beneficial in restoring RSC to normal and preventing irreversible sickling, which can lead to blood vessel occlusion, severe pain, severe anaemia from haemolysis of the ISC and end-organ injuries. Whilst we have achieved excellent results in seven patients over 20 years, translating this to an estimated 7–20 million patients globally requires a prospective cohort study and a cost-benefit analysis.

Acknowledgements (Graphics)

The authors would like to thank Isiuwa Omoigui, BA, Political Science, Ethnicity, Race and Migration (Yale'23) (Columbia Law School, New York).

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