



Special Communication

Improving Outcomes for Patients With Sickle Cell Disease in the United States Making the Case for More Resources, Surveillance, and Longitudinal Data

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Abstract

IMPORTANCE Although considered a rare disease with fewer than 200 000 cases annually in the US, sickle cell disease (SCD) is the most common and clinically significant inherited blood disorder in the US and worldwide. Despite the relatively high prevalence of this rare disease, there is a paucity of longitudinal data available to evaluate access to care or to identify quality metrics.

OBSERVATIONS This review discusses why systematic data collection for SCD through population-wide surveillance programs can help to facilitate progress in treatment. It also explores the importance of having both a longitudinal clinical registry and a national surveillance program to improve resource utilization, clinical outcomes, and provide an equitable foundation for care.

CONCLUSIONS AND RELEVANCE Federal funding should be appropriately allocated to establish and maintain a national SCD surveillance system supported by the Centers for Disease Control and Prevention, as well as a longitudinal registry available at recognized sickle cell centers.

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Introduction

Although considered a rare disease with fewer than 200 000 cases annually in the US, sickle cell disease (SCD) is the most common and clinically significant inherited blood disorder in the US and worldwide.¹ The complications of SCD may include increased risk for life-threatening infections, severe acute and chronic pain, silent and overt stroke, progressive organ damage, diminished quality of life, and shortened longevity. As with other chronic genetic diseases, identification of people with the condition, followed by proper institution of evidence-based therapies, can reduce disease burden, and promote cost-savings to the health care system. Herein, this report discusses why and how systematic data collection for SCD through population-wide surveillance programs can help to facilitate progress in treatment, and how the many types of registries and databases can be complementary to surveillance data, promoting an economy of scale in resource allocation.

The Unmet Needs of Individuals With SCD

While medical advances have reduced SCD child mortality in high-resource countries, most adults with SCD die before 50 years of age.^{2,3} Because SCD is a clinically heterogeneous autosomal recessive disease, individuals with the same sickle genotype may have differing clinical manifestations—some patients with minimal symptoms in childhood develop more severe outcomes in adulthood, while others exhibit severe complications that began in infancy.^{4,5} Health care utilization and expenditures are high because of the consequences of acute and chronic complications of SCD.⁶ Additionally, the disease burden to the patient imparts a shortened lifespan and the loss of potential income, in addition to a substantial detriment to the quality of life.^{7,8}

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Despite the substantial personal and societal burden of SCD, compared with other genetic disorders SCD has received relatively little attention and minimal resources since it was first described in 1910. Investments in discoveries and clinical care infrastructure have been limited and have not kept pace with other equally devastating but less common inherited conditions. Cystic fibrosis (1.8 cases per 10 000 births) and hemophilia (2.3 cases per 10 000 male births) both have a lower incidence than SCD (4.9 cases per 10 000 births) but receive substantially more clinical and research funding dollars (Table).⁹⁻¹² In the US, most individuals with SCD are part of a racial or ethnic minority group (primarily Black individuals), are economically disadvantaged, experience limited access to health care (ie, few SCD specialists and treatment programs available), and encounter institutionalized racism and stigmatization.^{8,13-16} The lack of SCD awareness, attention, and federal investment is a product of a health care system and a political climate that deprioritize diseases affecting vulnerable underrepresented populations.⁹

The lack of financial resources for SCD has meant an insufficient number of clinicians adequately trained to provide SCD treatment for the population, especially clinicians for adults living with SCD.^{17,18} The paucity of adult-focused SCD clinicians may be associated with the limited exposure to SCD during adult hematology-oncology fellowships, poor reimbursement for providing care for patients with SCD (compared with oncology), and lack of federally funded comprehensive SCD centers able to support affected patients.¹⁸ The lack of clinicians for adults with SCD is compounded by the progressive and cumulative damage of SCD, including bone damage, chronic pain, cognitive dysfunction, kidney disease, priapism, pulmonary hypertension, and skin ulcers, as well as other complications. All of these complications occur more commonly in adults and require the involvement of multiple subspecialists for adequate management. Therefore, many adults living with SCD remain poorly treated, placing them at increased risk of complications. Compared with other inherited conditions, such as hemophilia and cystic fibrosis, adults with SCD often become lost in the health care system and are not able to find optimal therapy.^{19,20}

Lack of Population-Based Data

A key downstream consequence of the paucity of funding for SCD in the US is the lack of both a national SCD surveillance system and a national longitudinal clinical registry. These data systems are not mutually exclusive but instead provide complementary, necessary information. If well developed, a SCD surveillance system would incorporate all individuals with SCD regardless of payer, including those not seen in established SCD care centers, and would determine the true SCD prevalence and geographic distribution of individuals with SCD. A longitudinal clinical registry, on the other hand, would include a subset of the individuals in the surveillance system with more in-depth information, including laboratory and radiographic findings, as well as patient-reported outcomes. Ideally,

Table. Comparison of the Financial Support vs Need of 3 Prevalent Rare Genetic Diseases in the US

Genetic disease	No. of persons affected	No. of specialty centers	National registry and surveillance system status	Federal funding and expenditures per year
Sickle cell disease	100 000	30 Recognized by the NASCC ^a	To date, no national registry. In 2021, the Sickle Cell Data Collection program, a CDC-funded surveillance system, was established in 11 states.	Federal funding for research: \$812 per patient. ⁹ Foundations/nonprofit expenditures: \$102 per person. ⁹
Cystic fibrosis	30 000	280 Accredited by the CFF	In 1986, a national CFF patient registry was established with records for 81%-84% of patients. ¹⁰ To date, no national surveillance system.	Federal funding for research: \$2807 per person. ⁹ CFF expenditures: \$7690 per person. ⁹
Hemophilia	30 000	140 Federally recognized HTC	In 2011, Community Counts, a combined registry and surveillance system, was established with federal and private funding and includes HTC population profiles and the RBDSMR.	Federal funding for clinical care ^c : \$35 000 per center. The 340B program also supports >90% of HTC staff. ¹¹

Abbreviations: CDC, Centers for Disease Control and Prevention; CFF, Cystic Fibrosis Foundation; HTCs, Hemophilia Treatment Centers; NASCC, National Alliance of Sickle Cell Centers; RBDSMR, Registry for Bleeding Disorders Surveillance and Mortality Reporting.

^a Data from <http://www.sicklecellcenters.org>.

Applications for comprehensive SCD centers not yet included in this number.

^b Funding for sickle cell disease and cystic fibrosis (2008-2018).

^c Funding for hemophilia (estimated 2021) data from <https://www.hemophilia.org/advocacy/federal-priorities/federal-programs>.

information from the surveillance system and clinical registry would be linked, an imperative for a systematic and comprehensive understanding of the natural history of this disease, its outcomes, and trajectory under different care models. Importantly, both systems of assessment are necessary to improve outcomes for patients with this disease.

Without surveillance data, a true understanding of the implementation of disease modifying therapy is not possible. These data are also needed to ensure accurate estimates of resource allocations to mitigate the high cost of acute care utilization and the real risk of premature death owing to a lack of adequate preventative treatment. This is especially important for the underrepresented populations disproportionately affected by SCD in the US—Black and Hispanic communities that may not be identified without surveillance data.

There are both ethical and financial arguments for improving the understanding of SCD epidemiologic information. Without the foundational data that a systematic surveillance system would provide, it is difficult to establish true national health priorities as well as a contemporary understanding of the natural course of the disease for all individuals with SCD, not just for those affiliated with SCD centers. In other words, without surveillance data, it is impossible for SCD clinicians and researchers to know how to improve the quality of care for this disease at the population level.

The Value of Surveillance for Rare Diseases

Public health surveillance is the continuous, systematic collection and analysis of health-related data.²¹ Disease surveillance is important for rare diseases associated with premature mortality or which may impart a high emotional or economic burden on those affected or on the health care system. Of greatest importance is the need to understand where patients are receiving care, the quality of that care, health outcomes at the population level, trends in health outcomes over time, and health disparities.

In addition, the lack of disease surveillance may delay the diagnosis of rare comorbid complications that can be sufficiently evaluated only with large data sets (eg, the worse outcome of cancer in persons with SCD).²² Furthermore, as new therapies are developed for these rare conditions and translated into clinical care, it is imperative to evaluate their positive and negative impacts at the population level. These data cannot be obtained using 1 data set (eg, individual hospital electronic health record data) and instead require multiple sources of combined, linked, and deduplicated data. Without meaningful all-encompassing surveillance data, it is impossible to measure population impact.

In 2020, the National Academies of Science, Engineering, and Mathematics published a report titled *Addressing Sickle Cell Disease: A Strategic Plan and Blueprint for Action* which summarized the current challenges to providing high-quality care to individuals living with SCD and highlighted the specific areas where improvement is needed.²³ Implementation of a national SCD surveillance system was among the first areas identified for improving care and outcomes for individuals with SCD. Chronic disease surveillance must include both the analysis and the dissemination of collected data from multiple sources to provide a broad understanding and awareness for health conditions. Thus, SCD surveillance is paramount to enhancing awareness as well as evaluating the implementation of preventative health measures at the population level.

Pilot SCD Surveillance Programs

As the initial effort to develop a SCD surveillance system in the US, the Registry and Surveillance System for Hemoglobinopathies (RuSH) program was an interagency agreement between the Centers for Disease Control and Prevention's (CDC) Division of Blood Disorders and the National Heart, Lung, and Blood Institute.²⁴ During this 2-year project (2010-2012), 7 states identified and

collected data on people living with SCD. The program contributed previously unknown information, such as the incidence and prevalence of SCD in these 7 states and further demonstrated the use, complexity, and limitations of linking multiple data sources—newborn screening, vital records, clinical case reports, and administrative data—for understanding SCD morbidity and mortality trends, clinical characteristics, and health care resource utilization and identifying unmet needs.²⁵⁻²⁷

Because of limited funding,²⁴ following RuSH, the CDC's Public Health, Research, Epidemiology, and Surveillance in Hemoglobinopathies (PHRESH) project only continued surveillance work in California and Georgia. Designed to further validate SCD case definitions and data integration methods as well as to disseminate SCD surveillance data, PHRESH refined the surveillance definition of SCD and demonstrated the use and challenges of studying SCD using administrative data.²⁸ The initial efforts of the RuSH and PHRESH projects increased knowledge of the disease burden, use of acute health care resources, and mortality among the SCD population.^{19,29,30} These projects had 3 foundational outcomes: (1) underscored the benefits of multiple states sharing methodologies, ideas, and resources in a coordinated collaborative; (2) found ways to leverage SCD surveillance data (using combined data sources) to improve the lives of people living with SCD; and (3) identified the challenges pertaining to the lack of resources needed to conduct SCD surveillance and the variability of the data sources across time and states. These outcomes were best exemplified in California where they spurred positive changes in health policy. The California SCD surveillance project demonstrated a larger than previously expected number of persons with SCD living in areas where care was insufficient. The rise in both awareness and dissemination of these findings informed advocacy and subsequent legislation and appropriations, increasing funding of clinical resources for people with SCD. In California, \$15 million was allotted for enhanced care of adults with SCD.³¹ These findings also highlighted the areas of additional data that were necessary to adequately perform disease surveillance, specifically Medicare data, which was too expensive to procure at the time.

Building on the initial accomplishments of RuSH and PHRESH, the Sickle Cell Data Collection (SCDC) program was established in 2015.³² Funded by the CDC Foundation, through partnerships with multiple donors, SCDC allowed California and Georgia to collect and analyze additional years of data and disseminate the study findings to stakeholders, including health care clinicians and public health professionals, policy makers, and people living with SCD and their families. However, the lack of a continuous, legislatively directed funding stream limited the long-term viability of the project as well as the continuous provision of knowledgeable personnel whose roles remained tenuous without a guarantee of funding. Despite these challenges, the efforts were continued through donations, and these data have been used to raise SCD awareness and to inform researchers, stakeholders, and clinicians about the natural course of SCD and to highlight the many areas where additional information and follow-up are needed.^{20,26,33} Importantly, these findings more clearly demonstrated the health inequities for those living with SCD compared with other similarly severe, inherited, and less-common diseases.

Recent Efforts to Expand SCD Surveillance

The Sickle Cell Disease and Other Heritable Blood Disorders Research, Surveillance, Prevention, and Treatment Act of 2018 became Public Law 115-327 on December 18, 2018.³⁴ This law allows for grants "to improve data on the incidence and prevalence of heritable blood disorders, including SCD, and the geographic distribution of such diseases and conditions," essentially authorizing the SCDC program. However, there were no appropriations attached to the new law, which makes it difficult to accomplish. To remedy this problem, in 2019, persistent advocacy efforts by committed SCD stakeholders led to provision of 1 year of funding provided primarily by discretionary funds from the US Health and Human Services (HHS) Office of Minority Health and the CDC Office of the Director that allowed for an additional 7 states to receive training on SCD surveillance capacity building.³⁵

While this 1-year training program was taking place, SCD advocacy and professional organizations continued to engage with policy makers to request CDC-specific appropriations for the

activities described in Public Law 115-327. Although SCDC appropriations were not included in that year's Congressional Budget, an additional year of discretionary funding was secured in fiscal year (FY) 2020 from a conglomerate of sources, including the HHS Office of Minority Health, the CDC Office of the Director, and various centers throughout the CDC, the CDC Foundation, and Centers for Medicaid & Medicare Services. This 1-year allotment is currently being used to fund 11 states' SCDC data collection and sharing activities.

Finally, in FY 2021, the HHS budget contained some appropriations for SCD surveillance to be provided by Congress.³⁶ Although it is not yet the national surveillance system that is needed, it is a marked improvement in the sporadic, unreliable year-to-year funding, and a referendum on the value of surveillance for the SCD population. Expansion of the surveillance program to include all 50 states remains elusive but is a necessary goal. The estimated annual budget for a national comprehensive SCD surveillance program is \$25 million.³⁶

SCD Surveillance and Clinical Registry

While advocates and stakeholders continue to lobby for a national SCD surveillance program, a clinical longitudinal registry is also needed. A longitudinal registry has both real time clinical benefits for patients and provides granular real-world data on both individual and aggregate characteristics of persons living with SCD from patient-reported outcomes, among other data sources. Importantly, a clinical registry for SCD that begin by tracking individuals identified during newborn screening (eg, birth cohort) would ensure that young children receive necessary vaccinations and early-screening interventions, such as sickle stroke surveillance.³⁷ Because all children in the US undergo newborn screening for SCD, the opportunity to include infants with SCD in a registry is clear. Clinical registries can facilitate targeted drug and therapy development, assist in postregulatory approval and comparative effectiveness studies, improve disease understanding and predictive analytics, and identify better quality indicators of different treatments. A clinical registry can also help to interpret and validate findings from surveillance data. For instance, a registry may show that some patients are missed with the surveillance methodologies used to identify those with SCD, or that there is misclassification (eg, persons with SCD having sickle cell trait or a nonrelated anemia). A clinical registry, however, will not preclude the need for SCD surveillance because clinical registries mostly provide information on the patients accessing health care in designated clinical treatment centers and are not representative of the entire population of individuals with SCD. This is especially true in the case of SCD, where many individuals with the condition do not receive their health care in a specialized SCD center.^{38,39} Often SCD centers are the only locations that have the staff or resources to input data into a clinical registry, thereby excluding individuals not receiving care in centers. In addition, patients with SCD may use different facilities for their care and centers may not have those multisite data to include in a registry. In contrast, the population-level SCD surveillance data provide a robust assessment of the true burden of SCD (regardless of SCD center affiliation) and can highlight areas where comprehensive care is lacking. These data allow for inclusion of patients regardless of where they receive care because of the rigorous deduplication and linkage techniques used during population-based surveillance data collection and cleaning.

Exemplifying how surveillance and registry data are complementary, registries and natural history cohort study data have demonstrated a substantial increase in the frequency of hospitalization among young adults for greater disease severity and early mortality.^{20,40,41} These findings are complemented by SCD surveillance data that have shown that less than half of the population living with SCD is receiving necessary disease-modifying therapy, which only compounds negative health outcomes among young adults.^{32,42} The use of surveillance data concomitant to a clinical registry has been well documented in the treatment and management of hemophilia.⁴³ Like SCD, hemophilia is an inherited blood disorder that affects approximately 30 000 individuals in the US. Unlike with SCD, the CDC has directed funding for continuous hemophilia surveillance. In addition, Hemophilia Treatment Centers receive direct federal funding (through the Health

Resources Service Administration) and indirect federal funding through 340B programs⁴⁴ to support ongoing data collection for their registries as well as the necessary uncompensated clinical services needed for their patient population (Table). The Veterans Health Care Act of 1992 designated federally-funded Hemophilia Treatment Centers as covered entities eligible to participate in the 340B Drug Pricing Program in order to stretch their federal grant funding to provide comprehensive services to all patients served by the centers.¹¹ The hemophilia surveillance system captures basic individual data on individuals affected by hemophilia, which allows for a general understanding of the population size and patients' demographic information and characteristics. The corresponding registry does not include everyone in the surveillance system but instead requires a consent to collect more specific, individualized data that includes treatment information, patient reported outcomes, laboratory assays for factor deficiency, and other important disease characteristics.⁴³ In tandem, the surveillance data tells the broader story, while the registry provides the finite details.

Similarly, findings in cystic fibrosis highlight the many benefits of a clinical registry and shed light on the important funding disparity with SCD. Cystic fibrosis, like SCD, is an inherited condition now diagnosed by newborn screening in all 50 states. The cystic fibrosis registry, which has been in place since 1986, provides detailed demographic information individuals living with cystic fibrosis to patients, clinicians, and researchers.¹⁰ The Cystic Fibrosis Foundation Patient Registry (CFFPR) has allowed for robust quality improvement, including care guidelines with recommended nutrition and antibiotics, as well as disease-modifying therapies for the pulmonary and gastrointestinal complications of the disease.^{45,46} The target population for the CFFPR is everyone with cystic fibrosis in the US; however, the registry is estimated to account for only 81% to 84% of the population of individuals with cystic fibrosis.¹⁰ The discrepancy is because of inherent exclusion of patients not seen at least annually by an accredited cystic fibrosis care center and patients who do not consent to data collection.^{47,48} Efforts to provide national surveillance data for cystic fibrosis have demonstrated that the disease occurs more frequently than previously thought among populations of non-European descent.⁴⁸ In addition, population health data for cystic fibrosis continues to demonstrate improved long-term survival. These surveillance data are used in combination with the cystic fibrosis registry to identify predictors of improved outcomes and disease burden across a large population of affected people.^{49,50} However, the CFFPR is exceptionally representative of its patient population because of its breadth and size and because of intensive efforts to procure funding. Comparisons with SCD show immense disparity in overall funding from federal as well as foundation resources (ie, Cystic Fibrosis Foundation; Table).

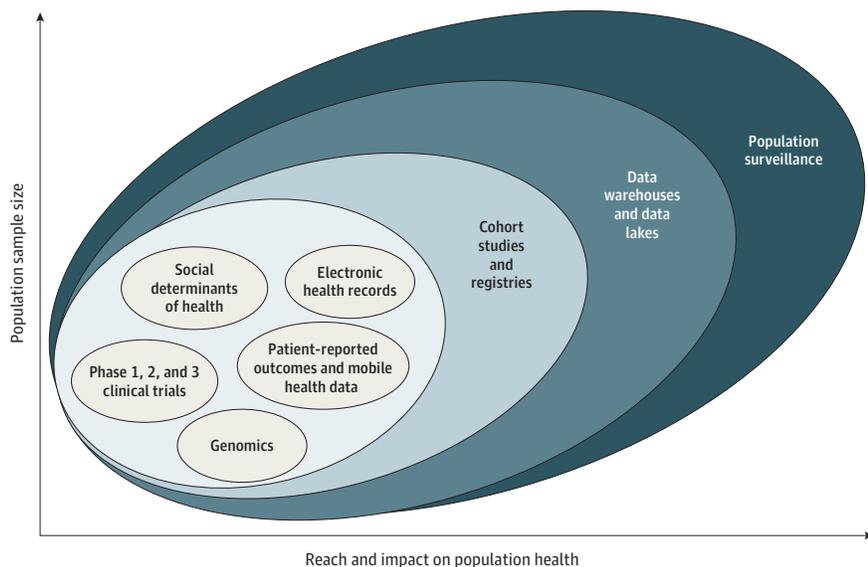
The examples from cystic fibrosis and hemophilia illustrate how investment in multiple streams of data collection imbedded within the understructure of surveillance promote a better understanding of the disease burden among a population and increase the reach of interventions that influence population health (**Figure**); this is especially true when data collection and analysis are coordinated. Analysis of surveillance data can reveal disease trends and patterns at the population level that cannot be seen at the local, institutional, or state level in rare disease registries. For instance, partnerships among surveillance programs and SCD treatment centers could allow for data harmonization among patients disconnected from evidence-based treatments and patients included in clinical registries (more likely to receive care at a center), thus addressing the inclusion bias. Specifically, because participation in clinical registries requires informed consent but HIPAA requirements are waived for authorized public health surveillance programs (under 45 CFR 164.512[b]), these partnerships can also be used to determine if patients who have consented are representative of the overall population in care. Finally, population surveillance data serve as the source for other studies, such as genomics studies, patient-reported outcomes analyses, and clinical trials (Figure). Clinical trials can benefit from the broad surveillance information made available by providing contextual data that can help to explain differences in intervention efficacy (not explained by the intervention mechanism) or facilitate the selection of appropriate study candidates in different geographic regions. Therefore, surveillance data can launch other studies, providing greater reach and affecting population health more substantially.

Conclusions

Given the importance and power of systematic surveillance data, it is clear that a national SCD surveillance system should be funded by the US Congress to be used in conjunction with a longitudinal clinical registry or registries for SCD, as recommended by the National Academies of Science, Engineering, and Medicine.²³ This surveillance-registry partnership would provide data for assessing access to health care by patients affiliated with SCD centers vs those unaffiliated, identifying discrepancies among different levels of care, elucidating how evidence-based treatments are being consumed, and showing how population-level trends (eg, mortality, health care utilization) respond to changes in SCD care access, policies, therapies, and implementation of guidelines. Just as with hemophilia, SCD surveillance data should be collected and maintained by the CDC, expand the SCDC program and further enhancing it by arranging for the Centers for Medicaid & Medicare Services to require that data be shared with it. Additionally, the 340B program should be modified to include a specific SCD indication. The newly formed National Alliance for Sickle Cell Centers could use and distribute funding for data collection at recognized comprehensive SCD centers (sicklecellcenters.org). This new organization is providing criteria by which to recognize comprehensive sickle cell centers that follow evidence-based practice guidelines and is promoting the adoption of standards of care associated with improved patient outcomes and quality of life. Funding from 340B programs would support data collection and provide more SCD-focused clinicians and required SCD supportive care services. Currently, enrollment in the existing registry is part of an unfunded mandate to improve the quality of care for individuals with SCD. With funding, all consenting patients would have their data entered by an SCD center coordinator into the centralized registry. Mirroring the successful efforts of the Cystic Fibrosis Foundation, the data would come from information available in patient’s medical records and from patient- or family-reported outcome assessments. Furthermore, 340B funding could deliver equitable supportive services for individuals with SCD, as it does for those with hemophilia.

Most importantly, the SCD surveillance-registry partnership would avoid redundancy among national clinical databases and would accelerate knowledge gains and better inform resource allocation for SCD research, legislation, and health care. A national SCD surveillance program that makes its findings available to all stakeholders (patients, health care clinicians, researchers,

Figure. Population-Based Surveillance Data as the Basis for Other Studies



Relationships among the individual data sources and population-based data underscore how surveillance data encompass all other data sources. Because population surveillance includes all individuals in the population, it serves as a platform on which other studies can be built and generalized to other populations. A data lake is a centralized repository that allows storage of all structured and unstructured data at any scale.

legislators, advocates) would make it possible for the US to finally begin to address the health disparities imperiling individuals living with SCD.

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