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# Chapter 7: Looking Forward

The process of developing guidelines for the management of persons with SCD has been challenging, as high-quality evidence is limited in virtually every area related to SCD management. The systematic review of the literature identified a very small number of RCTs in individuals with SCD (for example, only three evaluating hydroxyurea, one of the most promising treatments), clearly demonstrating the extensive knowledge gaps in SCD and care of individuals with SCD.

## New Research Is Needed

Cure is always the most desirable outcome for any chronic disease. Therefore, research that increases the evidence for and availability of a cure for SCD is a high priority. Hematopoietic stem cell transplantation (HSCT, formerly called bone marrow transplantation) is a treatment option for an increasing but still small number of people with SCD. The procedure involves “conditioning” therapy, utilizing myelosuppressive and/or immune-modifying drugs, followed by infusion of histocompatible stem cells (derived from bone marrow, peripheral blood, or umbilical cord blood). Substantial risks are involved with the procedure, and it is not yet feasible in the majority of people with SCD. Although clinical trials have provided promising results, and cure appears to be possible in a large proportion of patients receiving HSCT,<sup>427</sup> additional research is still needed that addresses the potential risks of this therapy (e.g., failure of engraftment and chronic graft-versus-host disease) before HSCT can become a widely used therapy.<sup>428</sup>

Additional research is also required to address the many other areas with little or no evidence that were identified during the development and writing of these guidelines. The needed studies include observational work to better describe the utility of screening asymptomatic individuals with SCD for commonly occurring chronic diseases; studies to better describe the clinical course of the occurrence and treatment results of all the acute and chronic complications of SCD; comparative effectiveness studies to provide clear outcomes on best approaches to SCD and its complications; clinical trials for new therapeutic approaches or to improve on current therapeutic approaches such as examining the role of hydroxyurea in people with genotypes and clinical manifestations other than those in the MSH study or transfusion goals in chronic conditions. A few of the other larger research agenda issues, in addition to the need for an SCD cure, are summarized below.

## Data Systems That Meet the Highest Standards of Scientific Rigor Can Be Invaluable Resources

Well-designed databases with linked biorepositories are required to complete observational studies and enable investigators to generate and test specific hypotheses. The databases must include longitudinal information on patient outcomes, therapies, health care services received, and the health system context in which the services were provided. The patient cohorts must be well-characterized by genotypic and phenotypic data. For example, this might be facilitated by mobilizing the Nation’s diverse newborn hemoglobinopathy screening programs to pool and analyze their data. Some of these State-supported and academic center-based programs already have assembled valuable information on treatment and long-term outcomes of individuals identified as having SCD, which could be leveraged for the longitudinal studies.

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## Improved Phenotyping Is Needed

The new expanded databases and data systems should enable the development of clinical and perhaps health care resource utilization phenotypes of individuals with SCD. Phenotyping includes the characterization of specific clinical, laboratory, imaging, and health care utilization features unique to some but not all individuals with SCD. Phenotypes require development of specific terminology to make such phenotyping as precise as possible. Phenotyping will require expanded collaboration among specialists in multiple disciplines to aggressively participate in and lead SCD-related research.

## Broad Collaborations for Research and Care

SCD is a chronic condition that impacts every part of a person's body and most aspects of their daily life. Research regarding such conditions requires broad-based expertise. This process has begun to take shape during the past decade, with neurologists, pulmonologists, behavioral scientists, and health services researchers using their unique training and tools to improve SCD management. The communities of pain specialists, epidemiologists, informatics experts, and basic and translational scientists should come together to develop the framework for future management guidelines for SCD.

## Beyond Efficacy: From Bench to Bedside and the Community

Perhaps the largest need is to translate the results of research that has been performed in laboratories and academic centers into community-based practice tools and clinical protocols. Such translational studies should lead to effectiveness trials. "Efficacy" does not always translate to "effectiveness." One of the best examples is hydroxyurea. Although hydroxyurea has proven efficacious in RCTs, the majority of eligible persons with SCA in the United States do not yet receive this agent. Well-designed effectiveness and translational studies are needed to overcome the identified barriers that result in underutilization of hydroxyurea. These barriers include the limited number of physicians with knowledge and experience with the agent, and patients' misconceptions and fears about side effects. Studies are also needed to examine the role of hydroxyurea in people with genotypes and clinical manifestations other than those in the MSH study.<sup>9</sup> The SCD research community can make a real difference through comparative effectiveness research and other investigative strategies, as well as strengthening clinical and public health SCD collaborative efforts at the State and local levels. Finally, all of the research addressed in these guidelines cannot be successful for the approximately 70,000 to 100,000 individuals with SCD in the United States until sickle cell centers, practicing hematologists, and primary care providers in particular are fully willing and capable of taking on the challenges of serving these individuals and their families.

The expert panel realizes that these guidelines leave many uncertainties for health professionals caring for or planning to begin caring for individuals with SCD. However, we hope that these guidelines begin to facilitate improved and more accessible care for all individuals with SCD, and that the discrepancies in the data will trigger new research programs and processes that will provide the evidence necessary to expand upon evidence-based SCD guidelines in the future.