Published in final edited form as:

*Genet Med Open*. 2024 ; 2: . doi:10.1016/j.gimo.2023.100838.

# A scoping review exploring cure definitions and language for inherited hemoglobinopathies

**Marilyn S. Baffoe-Bonnie**[1,2,3], **K. Jameson Floyd**[1], **Alicia A. Livinski**[4], **Christine Grady**[2,*]

[1]Health Disparities Unit, Social and Behavioral Research Branch, National Human Genome Research Institute, Bethesda, MD

[2]Department of Bioethics, National Institutes of Health Clinical Center, Bethesda, MD

[3]Department of Sociology, Rutgers University, New Brunswick, NJ

[4]National Institutes of Health Library, Office of Research Services, Office of the Director, National Institutes of Health, Bethesda, MD

## Abstract

**Purpose:** Sickle cell disease and beta thalassemia are some of the first targets for potentially curative cell-based therapies. Currently, bone marrow transplants, stem cell transplants, and gene therapy are being researched and utilized for people living with these hemoglobinopathies. Although these therapies are often described as curative, there is not a clear definition of what cure means for these hemoglobinopathies.

**Methods:** Five databases were searched for this scoping review. Two reviewers screened each article at the title/abstract and full text levels using Covidence. Articles were included if they were (1) about bone marrow transplants, stem cell transplants, or gene therapy; (2) conditions of focus were sickle cell disease or beta thalassemia; and (3) reported original data on clinical outcomes, psychosocial outcomes, or key stakeholder perspectives and opinions. Data were collected by 2 reviewers also using Covidence, and analyses were conducted in Excel and R.



*Correspondence and requests for materials should be addressed to Christine Grady, National Institutes of Health Clinical Center, Bioethics, Building 10/1C118, NIH, Bethesda, MD 20892-1504. cgrady@cc.nih.gov.

Conceptualization: M.S.B.-B., K.J.F., C.G., A.A.L.; Methodology: M.S.B.-B., K.J.F., C.G., A.A.L.; Formal Analysis: M.S.B.-B., K.J.F., C.G., A.A.L.; Writing-original draft: M.S.B.-B.; Writing-review and editing: M.S.B.-B., K.J.F., C.G., A.A.L.

The Article Publishing Charge (APC) for this article was paid by the NIH Clinical Center.

Ethics Statement

This material is the authors' own original work, which has not been previously published elsewhere. The paper is not currently being considered for publication elsewhere. The paper reflects the authors' own research and analysis in a truthful and complete manner. The paper properly credits the meaningful contributions of co-authors and co-researchers. The results are appropriately placed in the context of prior and existing research. All sources used are properly disclosed (correct citation). Literally copying of text must be indicated as such by using quotation marks and giving proper reference. All authors have been personally and actively involved in substantial work leading to the article and will take public responsibility for its content.

Conflict of Interest

The authors declare no conflicts of interest.

Additional Information

The online version of this article (https://doi.org/10.1016/j.gimo.2023.100838) contains supplemental material, which is available to authorized users.

**Results:** We found that, although cure is widely and indiscriminately used, it is not often defined, and when cure is defined, there is no clear convergence or consensus on the definition. Furthermore, cure is often qualified and undefined euphemisms for cure are often used. We also report the major ways in which the success and complications of these treatment modalities are described.

**Conclusion:** We frame the significance of our findings by discussing their scientific, ethical, and social implications and focus on the need for precise and clear terminology that centers lived experience and acknowledges the interplay between scientific and lay expertise and perceptions.

### Keywords

Beta thalassemia; Cure; Gene therapy; Sickle cell disease; Transplant

## Introduction

There is significant stakeholder interest in the continued rapid advancement of disease-modifying and curative therapies for hemoglobinopathies. Hemoglobinopathies, such as sickle cell disease (SCD) and beta thalassemia, are some of the first monogenic diseases that are targets of novel therapies. SCD is caused by a single-point variation that causes red blood cells to take a crescent shape whereby causing the cells to stick together in blood vessels causing painful bone and joint crises, end-organ damage, and reduced life expectancy.[1] In beta thalassemia, hemoglobin beta chains are reduced or absent, causing a range of outcomes, including the reduced production of hemoglobin.[2] Individuals living with these diseases suffer from severe anemia that can cause weakness and fatigue, as well as increased susceptibility to infections.[1,2] Although both illnesses affect millions of people globally and are present in people of all descents, including, the Middle East and Asia, SCD is most prominent on the continent of Africa, and beta thalassemia is most prominent in Mediterranean regions.[3]

Despite the severity and high prevalence of these diseases, the primary therapeutic modalities are prophylactic and disease-modifying therapies, such as penicillin, hydroxyurea, and chronic blood transfusions.[1,2] At present, some stakeholders assert that bone marrow transplantation (BMT) and hematopoietic stem cell transplantation (HSCT), which replace an individual's stem cells with healthy donor-derived cells, are "potentially curative" options for SCD and beta thalassemia.[4] Gene therapies, which are still considered experimental for these conditions, are also categorized as "potentially curative."[5] Unlike BMT and HSCT, gene therapy does not require a donor and uses modified host cells whereby reducing the very severe potential risk of graft-versus-host disease (GVHD).[6]

Although some stakeholders assert that these therapies are curative, other stakeholders, including people who have gone through these therapies, argue that we ought to question the certainty with which these therapeutic modalities are described as curative.[7] These disagreements and the lack of an agreed upon definition of cure for SCD or beta thalassemia necessitates understanding how curative language has been used in scientific literature.[8] Such an inquiry is necessary because there is widespread and imprecise use of curative language in scientific, medical, and lay spaces.

To date, a systematic investigation into a definition of cure and the outcomes that suggest or question the accomplishment of cure for these inherited hemoglobinopathies has not been conducted. Therefore, to better understand how researchers use and define cure for SCD and beta thalassemia, we conducted a scoping review of peer-reviewed literature that reported original data on clinical outcomes, psychosocial outcomes, or key stakeholder perspectives and opinions related to BMT, HSCT, and gene therapy. People living with these illnesses and the larger public often hear about data that are reported in these peer-reviewed scientific publications. Furthermore, the scientific literature sets expectations and nomenclature for other researchers, patients, and the wider public.

Our primary aims are to (1) identify how often and in what ways curative and functional language (ie, non-physical and psychosocial language) is used in peer-reviewed scientific literature reporting on BMT, HSCT, or gene therapy for SCD and beta thalassemia, (2) describe the implicit and explicit definitions of cure used in scientific literature specific to SCD and beta thalassemia, and (3) highlight the successful outcomes and complications of treatment modalities as they are described. We describe the implications of our findings by highlighting the significant scientific, ethical, and social implications of utilizing curative language, especially when it is inconsistently defined.

## Materials and Methods

### Protocol and registration

We followed the Joanna Briggs Institute methodology for conducting a scoping review.[9] We wrote a protocol a priori following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) and for reporting this review.[10]

### Eligibility criteria

Articles were included if they were (1) about BMTs, stem cell transplants, or gene therapy, (2) conditions of focus were SCD or beta thalassemia, and (3) reported original data on clinical outcomes, psychosocial outcomes, or key stakeholder (eg, person living with illness, parent/guardian/family, or physician, researcher, or advocates) perspectives and opinions. Studies also had to be conducted all or in part in the United States and territories and written in English. Furthermore, studies had to use a cure-derived word (specifically, cure, cures, cured, curing, or curative).

Studies were excluded if they were reviews, clinical trial protocols, informed consent forms, gray literature, letters without data, commentaries/opinions, editorials, conference abstracts, conference papers, books, book chapters, dissertations, errata, corrigenda, corrections, assay studies, or used animals or cell lines. Studies were also excluded if the only intervention mentioned was gene editing. Studies that only focused on pre-transplant complications or interventions aimed to treat complications of transplant or gene therapy were also excluded.

### Information sources and search

A biomedical librarian developed the search strategy in consultation with the review team using keywords and controlled vocabulary terms for each concept of interest (SCD, beta thalassemia, bone marrow and stem cell transplants, gene therapy, and cure); see final search strategies in Supplemental File Search Strategies. The searches were completed in January 2022 in 5 databases: CINAHL Plus (EBSCOhost), EMBASE (Elsevier), PsycNET: PsycINFO and PsycARTICLES (American Psychological Association), PubMed (US National Library of Medicine), and Web of Science: Core Collection (Clarivate Analytics). Searches were limited to those published in English language, and a search strategy was used to exclude animal studies and publication types (eg, editorials, letters, commentary, protocols, and conference abstracts/proceedings).

### Selection of sources of evidence

We conducted 2 levels of screening using Covidence (Veritas Health Innovation). At level 1 screening, 2 reviewers (M.S.B.-B. and K.J.F.) independently screened only titles and abstracts based on the eligibility criteria. At level 2 screening, 2 reviewers (M.S.B.-B. and K.J.F.) independently screened the full texts of articles included after level 1 using the eligibility criteria. At both levels of screening, any disagreements between M.S.B.-B. and K.J.F. were resolved by C.G. and consensus discussion.

### Data collection, data items, and data synthesis

Data were collected from each article independently by 2 reviewers ([M.S.B.-B., K.J.F.]) using Covidence, with final decisions on discrepancies made by [C.G.] and consensus discussion. We collected authors, publication year, country in which the study was conducted, study funding source, study design, population, sample size, study aims, intervention studied, patient characteristics, key findings related to cure, and study outcomes. For data synthesis, data cleaning and analysis was done using Microsoft Excel, Microsoft Word, R Statistical Software (v4.2.2; R Core Team 2022), and RStudio (v2022.02.0; R Studio Team). The following R packages were utilized: tidyverse,[11] dplyr,[12] data.table,[13] packcircles,[14] ggplot2,[15] reshape2,[16] scales,[17] tidyr,[18] randomcoloR,[19] plyr,[20] stringr,[21] tidytext,[22] funModeling,[23] skimr,[24] janitor,[25] corrr,[26] devtools,[27] writexl,[28] and readxl.[29]

## Results

### Study selection and characteristics

A total of 1928 records were retrieved from the database searches of which 1037 were duplicates. 891 unique records proceeded to level 1 screening. After level 1 screening, 472 records were excluded because they did not meet our inclusion criteria (eg, absence of a cure-derived word, SCD, beta thalassemia, hemoglobinopathies, or a key therapeutic modality) leaving 417 records eligible for level 2 full text screening (the full text of 2 were not available). After completing level 2 screening, 353 records were excluded, leaving 64 records included and eligible for data collection. The 353 records were excluded for 8

reasons, including being review articles, not being conducted in the United States, and not reporting original data (see Figure 1).

Table 1 presents characteristics of the 64 included records. 56 studies were conducted in part or completely in the United States, and in 7 studies, the location was unclear. In 1 study, it was clear that it was conducted in the United States but also unclear whether it was conducted in other locations. Some studies did not mention their source of funding ($n$ = 27) or were funded through public sources (ie, government agency funding) ($n$ = 20). Of the 64 studies, bone marrow and stem cell transplantation encompassed 58 studies, 3 studies focused exclusively on gene therapy, and 3 studies focused on all modalities.

Studies that were only experimental were the most common type of study ($n$ = 26). However, a significant number of studies were designed as observational studies ($n$ = 24). Two studies were focused on economic evaluation and 10 studies had been all or in part qualitative. 47 of the studies focused only on SCD, whereas 10 focused only on beta thalassemia with the remaining studies focusing on both illnesses ($n$ = 7). Some studies centered various stakeholders. The majority of studies did focus only on people living with the illness as their central stakeholder ($n$ = 50); however, 15% of studies also focused on families and caregivers alone or in combination with people living with the illness ($n$ = 14). Studies focused on both pediatric (under 18 years of age) and adult (18 years of age and over) participants ($n$ = 34), adults only ($n$ = 15), pediatric participants only ($n$ = 12), or were unclear or did not mention who their study population was ($n$ = 4). In 1 study, it was clear that adults were involved, but it was unclear whether pediatric participants were also involved.

## Curative language

Table 2 depicts results related to the key findings of curative and functional language usage. Articles utilized cure language frequently. Although some studies used cure language only 1 to 5 times ($n$ = 37), some studies used cure over 21 times ($n$ = 6) with the highest usage being 37 times. The remaining studies used cure between 6 and 37 times ($n$ = 21). Cure qualifiers were defined as words added to cure language to further describe or modify its meaning. Figure 2 visually depicts the frequency of the various cure qualifiers with the size of the circle proportional to the number of times the qualifier was used. Of the various qualifiers used, “only” ($n$ = 27) and “potential/potentially” ($n$ = 19) were used most frequently. Some studies used qualifiers that described cure in ambiguous ways, whereas others described cure in more definitive ways. For example, although some studies describe cure as “experimental,” “emerging,” “with stipulations,” or “frustratingly elusive,” others described cure as “definitive,” “widespread,” and “established.” Studies also qualified the clinical aspects of cure. In some cases, cure was qualified to mean “phenotypic cure” or “hematopoietic cure.” In other cases, the biomedical outcome of cure was “toxic,” “high-risk,” or “radical.”

In addition to investigating the types of qualifiers that were used for curative language, we found that the majority of studies did not provide explicit definitions of cure ($n$ = 57). However, 7 studies explicitly defined cure (see Table 3). Of note is the definition of Salcedo and colleagues[30] that stated explicitly that a “fully effective cure (is) one that

completely suppresses disease-related complications and costs and restores life expectancy and health-related quality of life (HRQoL) to that of a comparable individual unaffected by the disease." This definition includes considerations of the economic impact of SCD and aspects of physical and functional outcomes.

Although most studies did not explicitly define cure, some studies provide language that suggested implicit understandings of cure. We identified uses of implicit curative language by focusing on words and phrases surrounding cure words. Implicit cure was discussed in several categories, including related to hematological functioning, disease-state, survival, and quality of life (see Figure 3 and Supplementary Table for Figure 3). We also found that studies frequently used various euphemisms ("cure-phemisms") to stand in as place holders for explicit curative language. For example, studies used phrases such as "disease-free," "get rid of the disease," "disease-reversal," and "free from sickle cell" as ways to allude to cure.

When implicit or explicit definitions of cure were provided, they usually focused only on the physical aspects of illness ($n = 16$). However, a few studies did recognize cure in ways related to elements of social/family, emotional, or functional aspects. Furthermore, some studies had other focuses such as financial, spiritual, and general quality of life.

## Functional language

Although we sought to identify how often and in what ways curative language was used, we also sought to investigate whether studies mentioned functional outcomes, defined as non-physical outcomes that were focused on non-physical aspects of HRQoL. Drawing on 3 of the 4 HRQoL domains found in the Functional Assessment of Chronic Illness Therapy measurement system, we assessed whether studies mentioned social/family well-being, emotional well-being, functional well-being, or some other type of non-physical well-being.[31] The Functional Assessment of Chronic Illness Therapy measurement system is a questionnaire that assesses the multi-dimensional health status of individuals living with chronic illness. Examples of social/family well-being are general social support questions such as feeling close to or supported by friends and family. Emotional well-being focuses on a participant's psychological condition, such as whether they feel sad, happy, or experience feelings of anxiety or hope. Finally, functional well-being is understood as the ability to perform daily tasks such as doing work or sleeping well.

More than half of the studies in our review did not mention any functional outcomes ($n = 41$). Of the 34% of studies that discussed functional outcomes, 19% focused on a combination of social/family well-being, emotional well-being, and functional-well-being, whereas the remaining articles reported a combination of social/family, emotional, functional, and other forms of well-being ($n = 12$) (see Table 2). Examples of other forms of well-being include reductions in opioid use, hospital visits, and the financial impact of illness.

## Success

As many studies used curative language but failed to define cure, we were also interested in understanding how outcomes of success and complications were described (see Figure 3). Closely linked to implicit understandings of cure are the general ways in which studies

describe success as it relates to these different therapeutic modalities. Therefore, we defined success outcomes as broader than cure such that they did not have to be discussed in the context of curative language. As Figure 3 depicts, some implicit understandings of cure also overlap with general descriptions of success.

There were several different markers of success including those related to engraftment, resolution or reduction of pain crises, low rates of GVHD, improved hematological outcomes (eg, normal hemoglobin levels and transfusion independence), and other outcomes related to the hallmark physical experiences of the illnesses beyond resolution of pain (eg, organ damage ceased or make disease less severe). Similar to most of the conceptions of cure, descriptions of success were primarily physical, although non-physical quality-of-life outcomes were sometimes mentioned (eg, no longer taking medication and "functional lives"[32]).

An exemplar study showing the interplay between cure definitions and success was conducted by Kodish and colleagues[33] that used the phrase "survival-cure." In this study, the authors assessed decisions about acceptable mortality risk in BMT by asking parents of children living with SCD what level of risk they would be willing to accept to achieve "survival-cure," which was defined as 100 percent probability of cure and 0-percent short term mortality. In this study, decision making was assessed at various probabilities of survival and cure. However, success was defined narrowly as cure in terms of survival. Furthermore, the authors recognize that they may not have given clear depictions of morbidity and the full range of possible complications beyond GVHD and organ-system complications.

## Complications

Although cure and success language were used widely and in positive ways, scholars reported significant complications associated with these therapeutic modalities. Although some studies reported actual complications experienced by participants, other papers focused on complications that could possibly happen. In these latter cases, participants expressed "fear of death or treatment failure."[34] In studies that reported experienced complications, the most prevalent complications were related to infection, GVHD, neurological functioning, mortality, and organ impairment (see Figure 3). Interestingly, a few studies also recognized reverting back to a disease-state as a complication. Although these complications have been reported in-depth in other research,[35] of interest is that in our review these complications were sometimes reported while still describing the modalities as successful and "curative," suggesting that success can at times be thought of as complicated success. For example, Mahesri and colleagues[36] described the rates of vaso-occlusive crises, transplant complications, and mortality in people living with SCD who had undergone BMT. They found that, although 138 of the 204 participants were crisis-free after 2 years, 55% of participants had transplant-related complications. The authors concluded that, although two-thirds of participants remained crisis-free, the transplant-related complications, including GVHD, occurred with high frequency suggesting that alternate therapeutic modalities with fewer complications are necessary.

## Discussion

Cure language in the context of therapeutic modalities for SCD and beta thalassemia is used frequently. However, there is no agreed upon definition of cure, and it is understood differently by various stakeholders, which has significant implications for how people understand what cure is. We conducted a scoping review of the peer-reviewed literature on bone marrow and stem cell transplantation and gene therapy for SCD and beta thalassemia that reported clinical outcomes, psychosocial outcomes, or perspectives of various stakeholders to understand how curative language is used to describe the outcomes of these interventions for inherited hemoglobinopathies. Our major finding that cure is used frequently but without a clear definition or consensus or convergence on what the definition is has scientific, ethical, and social implications.

### Scientific implications

Our first major finding was that cure language is used widely and indiscriminately in this scientific literature, and despite its widespread use, cure is not explicitly defined the majority of the time. When cure is defined, there are various and, at times, contradictory explicit and implicit definitions of cure. Such imprecision raises significant scientific implications for the field of therapeutic research for SCD and beta thalassemia. However, the scientific implications of using curative language have received limited attention in the field of these hemoglobinopathies.

We found that the majority of studies that implicitly or explicitly defined cure did so in physical ways. Similarly, success was often discussed in physical ways. However, in studies that did mention functional outcomes, the importance of these outcomes to the perception of cure and success were significant. For example, in a study by Gallo and colleagues,[7] who interviewed people living with SCD who had survived stem cell transplants, success and cure were described as coming with “stipulations.” Of the 9 participants who classified their transplants as a success or near success, only 3 explicitly classified their transplants as cure. For the other participants, there were aspects of their lived experiences that prevented them from feeling cured. For example, some participants who were still on anti-rejection medications or had minor pain did not feel comfortable calling their experiences cures. Although participants had successful transplants (as subjectively defined by the participant), their experiences of continuing to have pain and take medication are physical limitations that caused additional functional, social, and emotional limitations. Although these functional outcomes may not have been the primary outcomes of the studies in which they participated, they were central outcomes for the participants’ interpretation of holistic success and cure. As Gallo and colleagues[7] note, all participants, before the transplant, expected success and that the transplant would allow them to achieve central functional outcomes, such as pursuing life goals. Continuing a narrow focus on success and cure as solely related to disease-state discounts the psychosocial outcomes that people living with these illnesses deem important. Furthermore, this study shows that between scientists and the community of people who have undergone curative therapies, there are contestations over whether the experience should be classified as cure. As such, we urge scientists to think holistically and include measures of functional, psychological, and social outcomes

into their intervention designs as they continue to develop new therapeutic modalities for SCD and beta thalassemia.

The relationship between a reduction in physical suffering and an increase in quality of life and function is not always linear. For example, in some articles, despite having an initial or continued reduction in suffering caused by SCD, participants still struggled with chronic skin GVHD, complications of anti-rejection medications that were sometimes perceived as worse than sickle cell complications, and isolation during the recovery process.[7,37] In SCD and beta thalassemia, the longevity, durability, and long-term complications of experimental therapies is still being studied. Additionally, as we found in the explicit cure definition of Salacedo and colleagues, some stakeholders understand cure by its durability (as defined by the effects of a therapy lasting at different time markers such as for 5 or more years).[30] In another case, we find that some qualifiers such as “potentially” and “definitive” are contradictory in meaning as the former recognizes possibilities for complicated success or failure, whereas the latter does not. Here, interrogation into “cure-phemisms” is again helpful. In the case of bone marrow and stem cell transplants for SCD, what it means to “no longer have sickle cell” can be complicated because the potential for the presence of sickled cells and subsequent painful crises is possible depending on the therapeutic modality used.[38] For example, articles included in our review have shown that there is potential for individuals to have symptoms of SCD after bone marrow and stem cell transplantation.[38]

As funders and researchers seek to determine which research interventions to prioritize, it will be important to seek out those that recognize the dual importance of addressing and improving both physical and non-physical outcomes of therapies. Furthermore, as scientists define what scientific goals and outcomes ought to be prioritized, it will be important to understand what physical and non-physical tradeoffs participants are willing to live with post-therapy and to articulate the relative likelihood of such outcomes occurring. Although functional well-being can be improved by physical well-being, studies reviewed here also show that there are significant complications that prevent quality-of-life improvement even in the presence of biomedically defined physical improvement.

## Ethical implications

Miscommunication between medical researchers and health news reporting has been a long-recognized issue.[39] Researchers sometimes argue that media reporting does not accurately reflect research, whereas media reporters argue that research reports are not accessible to the public. Both issues result in sometimes irresponsible and limited public dissemination of medical research findings.[39] We strongly suggest that people living with hemoglobinopathies be centered in these conversations whether or not they have engaged or plan to engage with these interventions. This is because the scientific community, reporters, research participants, people living with hemoglobinopathies, and larger lay audiences are in a relational dynamic such that what information emerges from one group impacts information access and understandings in another group.

When people living with hemoglobinopathies are directly centered in conversations about health communication, concepts related to therapeutic and curative misunderstanding can help elucidate how unclear and imprecise terminology results in major ethical concerns

and other health communication issues. Research participants are thought to experience a therapeutic misconception when they do not understand the purpose of research, conflate it with care, and believe that a trial will help them personally.[40,41] Building on this concept, Rennie and colleagues[42] define "curative misconception" as when a participant falsely believes that they are guaranteed to be cured by an intervention. Therapeutic and curative misunderstanding are thought to interfere with informed and meaningful consent.[40]. There is also significant value in applying the concepts of therapeutic and curative misunderstanding to explore how various forms of misunderstanding could negatively affect the perceptions that many with access to research findings (eg, potential participants, media and science writers, and those living with the illness) have about these trials. These concepts are especially useful in the present case as a large proportion of reviewed studies were experimental.

In this review of scientific literature, curative language is sometimes qualified as "potential" and at other times described as "sure" or "successful." In only a limited number of cases do authors claim to have cured their participants. The few explicit definitions of cure range from being disease-free, survival and recovery (without discussion of whether survival is disease-free or event-free survival), and improvement in various quality-of-life outcomes. Although studies focus on different outcomes and endpoints, generalized and imprecise language in reporting could contribute to unrealistic expectations about both the meaning of, and the potential for, cure for various groups of people.

For example, participants who have participated in these trials may have their post-trial experiences affected by the language used in reporting these studies. If participants do not themselves feel cured, they may experience tensions between their perceived lived experience and how writers describe their experiences. Additionally, curative misconceptions may arise in people living with these illnesses who hope to participate in trials or access these therapies. They may believe that their participation would guarantee that they will be cured, although the purpose of science is to create generalizable knowledge. Finally, other scientists and journalists may be susceptible to misunderstanding if their perceptions of success and cure are shaped by research reports that use imprecise language.

Media articles that use unclear and imprecise curative language when they report on scientific progress for hemoglobinopathies may also contribute to general misunderstanding. For example, a recent New York Times article describing the experience of a young adult in an experimental gene therapy trial, described BMTs and gene therapy as cures. The individual is described as cured because "her symptoms have vanished" and she has been "declared free of the disease."[43] However, at the end of this article, the author notes that gene therapy clinical trial participants will only be considered "truly cured" if after a 15-year follow-up they remain free of sickle cell. Language used within this one article reporting on scientific progress suggests potential avenues for misunderstanding. For example, the New York Times article notes a difference between "cure" and "true cure" with the latter being contingent on time, unknown potential future complications, and durability. Future research ought to understand the relationship between clinical research language, scientific literature, journalistic reports, and misunderstanding among the general population and potential research participants.

Instances such as this suggest that scientific uncertainty is another key ethical implication, which other scholars have noted in the case of HIV/AIDS research.[44] Scientific uncertainty acknowledges that in the context of clinical research, there is significant uncertainty about risks and benefits of investigational therapeutics compared with that of established standard of care. For example, there were cases in HIV/AIDS literature in which participants in hematopoietic stem cell research and antiretroviral therapy administration soon after birth were presumed cured, although in both cases, they eventually had viral rebound.[44] Without a clear definition of cure and success that considers issues such as durability and participant perspectives on the various nuances of cure and success, there is a possibility that uncertainties related to the possible outcomes of investigational therapies could be overlooked or misunderstood. Furthermore, because published clinical research is used to translate information to the public, the recipients of communication with unclear definitions of cure or what outcomes describe cure may find themselves misunderstanding the stage, purpose, and outcomes of published research.

## Social implications

There are several social implications of our findings. We focus our discussion on the interplay between lived experience and biomedical constitutions of illness and success. Scholars have found in other cases that the ways in which biomedical experts understand disease varies significantly from the ways that those living with the illness and caregivers understand disease and, more importantly, what it means to be well.[45] In our study, we find evidence of such contestations, especially when looking at cross-study comparisons of cure language usage. For example, in some qualitative articles that are explicitly focused on functional well-being, we find that terms related to success and cure define cure in more general, experience-based language such as “live a normal life” and “not having to worry about taking medicine every day.”[37] However, in some clinically focused papers, scientists often describe success and cure in narrow biomedical terms such as “survival curves” without further consideration for non-physical outcomes.[46] Relatedly, in studies that do report clinical outcomes and quality-of-life outcomes, contestations between stakeholders still arise. In one study, although an individual’s clinical outcomes suggest success and cure, the individual, who underwent HSCT, still expresses hesitation about the presence of the underlying cause of their illness by saying that they worry if all of their sickle cells are “completely gone” or if “[their] sickle cell disease would be coming back.”[7] Such worries are recognized in clinical papers that recognize that cure may be attached to time and durability such that cure depends on “survival curves of these patients reach(ing) a plateau around 3 years after BMT and remain(ing) unchanged there-after”[46] or increments of 5, 10, and 15 years.[30]

People living with hemoglobinopathies’ perceptions of therapies are central to understanding how these therapies ought to be framed. Imprecise and undefined language may shape how the relative social benefit and value of these therapies are understood by people seeking therapeutic benefit. We found that the metrics used to define success outcomes ranged; although some studies reported success and cure as a complete absolution of painful sickle cell crises, in other studies, the metric was on a sliding scale, such that any outcome from less to no pain was considered a cure.[38] Rigid differences in descriptions of success leave

less room for varied clinical experiences of people who participate in therapies with curative intent although the clinical experience of people living with inherited hemoglobinopathies varies significantly.[47] Furthermore, potential issues related to participant perceptions of clinical expectations and benefits may arise when a person's lived experience stands in contrast with the definition of success and cure being utilized. For some participants, they may be unwilling to accept less pain and expect no pain as an outcome and may say that one option is unequivocally not a cure or success.

### Limitations and future avenues

We included only journal articles with original data about biomedical interventions for SCD and beta thalassemia as the majority of scientific journals are peer-reviewed thereby ensuring the originality, utility, and conduct of the published studies. However, such an approach does limit our understanding of how cure is defined in sources we excluded, such as media reports that may write about cure. Second, when extracting implicit cure definitions, we only chose to extract words and phrases that were in the context of cure language. As such, we may have missed language that alluded to cure (eg, "free from disease") if it was not associated with cure language. Although some euphemisms for cure, such as "disease-reversal," were repeatedly used, to adhere to our rigorous methodology, we did not go back and collect additional references of these euphemisms in other contexts. However, this is an avenue for future research because the implicit cure euphemisms used in some papers were used across studies. We only included English language articles as none of the review team members have capacity to read or translate other languages, thereby possibly limiting our understanding of the use and meaning of cure in non-English language contexts. Including additional languages would likely expand our understanding on how cure language is used and in a variety of contexts. For this review, we chose to not use language analytic tools because of concerns with accuracy of translation and interpretation.

There are several avenues for future research suggested by our findings. Future research should seek to center how people living with hemoglobinopathies in a global context understand the concept of cure because these individuals will be directly affected by emerging advanced therapies. Future research is also needed to understand how other stakeholders, such as physicians, scientists, legislatures, and the media understand cure. We also encourage scholars to use new measurements to better understand the range of physical and non-physical impacts of potentially curative therapies in order to have a more comprehensive understanding of the various domains of cure, success, and complications discussed in this review.

## Conclusion

Our findings suggest that there are contestations between stakeholders about what a cure for SCD or beta thalassemia is. However, as research continues in this area and additional novel therapies are researched, funded, and brought to market, clearly defining what is a cure for SCD or beta thalassemia will be of utmost importance for scientific, ethical, and social reasons. Therefore, we encourage further discussion and research into this area that centers

the experiences and perspectives of people living with these hemoglobinopathies who have and have not undergone these therapeutic modalities.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

The authors would like to thank Dr. Courtney Fitzhugh of the National Heart, Lung, and Blood Institute for her help in providing scientific terminology to include for the search terms related to BMTs, stem cell transplants, and gene therapy. The authors would also like to acknowledge all the people with SCD and beta thalassemia mentioned in the articles reviewed here.

### Funding

This work was funded by the National Institutes of Health Intramural Research Program.

## Data Availability

The raw/processed data required to reproduce the above findings are available upon request.

## References

1. Piel FB, Steinberg MH, Rees DC. Sickle cell disease. N Engl J Med 2017;376(16):1561–1573. 10.1056/NEJMra1510865 [PubMed: 28423290]
2. Fibach E, Rachmilewitz EA. Pathophysiology and treatment of patients with beta-thalassemia – an update. F1000Res 2017;6:2156. 10.12688/f1000research.12688.1 [PubMed: 29333256]
3. Thein SL. Genetic basis and genetic modifiers of β-thalassemia and sickle cell disease. In: Malik P, Tisdale J, eds. Gene and Cell Therapies for Beta-Globinopathies New York: Springer; 2017;1013:27–57. 10.1007/978-1-4939-7299-9_2
4. Smiers FJ, Krishnamurti L, Lucarelli G. Hematopoietic stem cell transplantation for hemoglobinopathies: current practice and emerging trends. Pediatr Clin North Am 2010;57(1):181–205. 10.1016/j.pcl.2010.01.003 [PubMed: 20307718]
5. Ferrari G, Cavazzana M, Mavilio F. Gene therapy approaches to hemoglobinopathies. Hematol Oncol Clin North Am 2017;31(5):835–852. 10.1016/j.hoc.2017.06.010 [PubMed: 28895851]
6. Leonard A, Tisdale J, Abraham A. Curative options for sickle cell disease: haploidentical stem cell transplantation or gene therapy? Br J Haematol 2020;189(3):408–423. 10.1111/bjh.16437 [PubMed: 32034776]
7. Gallo AM, Patil C, Adeniyi T, Hsu LL, Rondelli D, Saraf S. Health-related quality of life and personal life goals of adults with sickle cell disease after hematopoietic stem cell transplantation. West J Nurs Res 2019;41(4):555–575. 10.1177/0193945918768277 [PubMed: 29624126]
8. Hendriks S, Pearson SD. Assessing potential cures: are there distinctive elements of value beyond health gain? J Comp Eff Res 2021;10(4):255–265. 10.2217/cer-2020-0190 [PubMed: 33663230]
9. Peters MDJ, Marnie C, Colquhoun H, et al. Scoping reviews: reinforcing and advancing the methodology and application. Syst Rev 2021;10(1):263. 10.1186/s13643-021-01821-3 [PubMed: 34625095]
10. Tricco AC, Lillie E, Zarin W, et al. PRISMA extension for scoping reviews (PRISMA-ScR): checklist and explanation. Ann Intern Med 2018;169(7):467–473. 10.7326/M18-0850 [PubMed: 30178033]
11. Wickham H, Averick M, Bryan J, et al. Welcome to the tidyverse. J Open Source Softw 2019;4(43):1686. 10.21105/joss.01686
12. Wickham H, François R, Henry L, Müller K, Vaughan D. Dplyr: A Grammar of Data Manipulation 2023.

13. Dowle M, Srinivasan A, Gorecki J, et al. Package'data. table. Extension of 'Data Frame 2019:596.
14. Bedward M, Eppstein D, Menzel P. Packcircles: Circle Packing 2018.
15. Wickham H ggplot2. WIREs Computational Stats 2011;3(2):180–185. 10.1002/wics.147
16. Wickham H, Wickham MH. Package "reshape" 2015;7:1–10. https://cran.rproject.org/web/packages/reshape2/reshape2
17. Wickham H, Wickham MH, RColorBrewer I. Package "scales". R Package Version 2016;1(0).
18. Wickham H, Wickham MH. Package "tidyr". Easily Tidy Data with'spread'and'gather 'Functions 2017.
19. Ammar R randomcoloR: generate attractive random colors. R Package Version. 2019 2019;1(0.1).
20. Wickham H, Wickham MH. Package "plyr". Obtenido Httpscran Rproject Orgwebpackagesdplyrdplyr Pdf 2020.
21. Wickham H, Wickham MH. Package "stringr" [Web site] 2019. http://stringr.tidyverse.org. https://githubcom/tidyverse/stringr
22. Silge J, Robinson D. tidytext: text mining and analysis using tidy data principles in R. J Open Source Softw 2016;1(3):37. 10.21105/joss.00037
23. Casas P, Casas MP, Imports R. Package "FunModeling". Explor Data Anal Data Preparation Tool-Box 2020.
24. Waring E, Quinn M, McNamara A, De La Rubia EA, Zhu H, Ellis S. Skimr: Compact and Flexible Summaries of Data. R Package Version 2.1 2021;3.
25. Firke S Janitor: simple tools for examining and cleaning dirty data. R Package Version 2020;2(1).
26. Kuhn M, Jackson S, Cimentada J. corrr: correlations in R. R Package Version 04 2020;3:1–15.
27. Wickham H, Hester J, Chang W, Hester MJ. Package "Devtools" 2022.
28. Ooms J writexl: export Data Frames to Excel "xlsx"Format. R Package Version 2020:1.
29. Wickham H, Bryan J, Kalicinski M, et al. Package "readxl". Version 2019;13:1.
30. Salcedo J, Bulovic J, Young CM. Cost-effectiveness of a hypothetical cell or gene therapy cure for sickle cell disease. Sci Rep 2021;11(1):10838. 10.1038/s41598-021-90405-1 [PubMed: 34035408]
31. Webster K, Cella D, Yost K. The Functional Assessment of Chronic Illness Therapy (FACIT) Measurement System: properties, applications, and interpretation. Health Qual Life Outcomes 2003;1:79. 10.1186/1477-7525-1-79 [PubMed: 14678568]
32. Chaudhury S, Ayas M, Rosen C, et al. A multicenter retrospective analysis stressing the importance of long-term follow-up after hematopoietic cell transplantation for β-thalassemia. Biol Blood Marrow Transplant 2017;23(10):1695–1700. 10.1016/j.bbmt.2017.06.004 [PubMed: 28627425]
33. Kodish E, Lantos J, Stocking C, Singer PA, Siegler M, Johnson FL. Bone marrow transplantation for sickle cell disease. A study of parents' decisions. N Engl J Med 1991;325(19):1349–1353. 10.1056/NEJM199111073251905 [PubMed: 1922237]
34. Schulz GL, Kelly KP, Holtmann M, Armer JM. Navigating decisional conflict as a family when facing the decision of stem cell transplant for a child or adolescent with sickle cell disease. Patient Educ Couns 2021;104(5):1086–1093. 10.1016/j.pec.2020.10.011. patient. [PubMed: 33234442]
35. Arnold SD, Bhatia M, Horan J, Krishnamurti L. Haematopoietic stem cell transplantation for sickle cell disease – current practice and new approaches. Br J Haematol 2016;174(4):515–525. 10.1111/bjh.14167 [PubMed: 27255787]
36. Mahesri M, Schneeweiss S, Globe D, et al. Clinical outcomes following bone marrow transplantation in patients with sickle cell disease: a cohort study of US Medicaid enrollees. Eur J Haematol 2021;106(2):273–280. 10.1111/ejh.13546 [PubMed: 33155319]
37. Khemani K, Ross D, Sinha C, Haight A, Bakshi N, Krishnamurti L. Experiences and decision making in hematopoietic stem cell transplant in sickle cell disease: patients' and caregivers' perspectives. Biol Blood Marrow Transplant 2018;24(5):1041–1048. 10.1016/j.bbmt.2017.11.018 [PubMed: 29196076]
38. Pawlowska AB, Cheng JC, Karras NA, et al. HLA haploidentical stem cell transplant with pretransplant immunosuppression for patients with sickle cell disease. Biol Blood Marrow Transplant 2018;24(1):185–189. 10.1016/j.bbmt.2017.08.039 [PubMed: 28939451]

39. Shuchman M, Wilkes MS. Medical scientists and health news reporting: a case of miscommunication. Ann Intern Med 1997;126(12):976–982. 10.7326/0003-4819-126-12-199706150-00008 [PubMed: 9182476]
40. Horng S, Grady C. Misunderstanding in clinical research: distinguishing therapeutic misconception, therapeutic misestimation, and therapeutic optimism. IRB Ethics Hum Res 2003;25(1):11–16. 10.2307/3564408
41. Henderson GE, Churchill LR, Davis AM, et al. Clinical trials and medical care: defining the therapeutic misconception. PLoS Med 2007;4(11):e324. 10.1371/journal.pmed.0040324 [PubMed: 18044980]
42. Rennie S, Siedner M, Tucker JD, Moodley K. The ethics of talking about '"HIV cure'", 2015/03/27 BMC Med Ethics 2015;16(1):18. 10.1186/s12910-015-0013-0 [PubMed: 25885856]
43. Kolata G Pioneering gene therapy freed her of sickle cell. Is a Cure at Hand? The New York Times 2023. https://www.nytimes.com/2021/09/14/health/sickle-cell-cure.html?action=click&pgtype=Article&state=default&module=styln-sickle-cell&variant=show&region=MAIN_CONTENT_1&block=storyline_top_links_recirc
44. Dubé K, Kanazawa J, Taylor J, et al. Ethics of HIV cure research: an unfinished agenda. BMC Med Ethics 2021;22(1):83. 10.1186/s12910-021-00651-1 [PubMed: 34193141]
45. Epstein S Impure science : AIDS, activism, and the politics of knowledge. Med Soc (Berkeley). University of California Press; 1996:1–466.
46. Gaziev J, Sodani P, Polchi P, Andreani M, Lucarelli G. Bone marrow transplantation in adults with thalassemia: treatment and long-term follow-up. Ann N Y Acad Sci 2005;1054:196–205. 10.1196/annals.1345.024 [PubMed: 16339666]
47. Steinberg MH. Predicting clinical severity in sickle cell anaemia. Br J Haematol May 2005;129(4):465–481. 10.1111/j.1365-2141.2005.05411.x [PubMed: 15877729]
48. Andreani M, Gregori S. The study of engraftment after hematopoietic stem cell transplantation: from the presence of mixed chimerism to the development of immunological tolerance. HLA 2018;92(suppl 2):57–59. 10.1111/tan.13402 [PubMed: 30270557]
49. Friedrich P, Steinfield E, Kim F, Hays MM, Lehmann L, Sprinz P. Lessons learned from talking with parents about the role of hematopoietic stem cell transplantation in the treatment of children with sickle cell disease. American Journal of Health Education 2015;46(3):144–156. 10.1080/19325037.2015.1021059

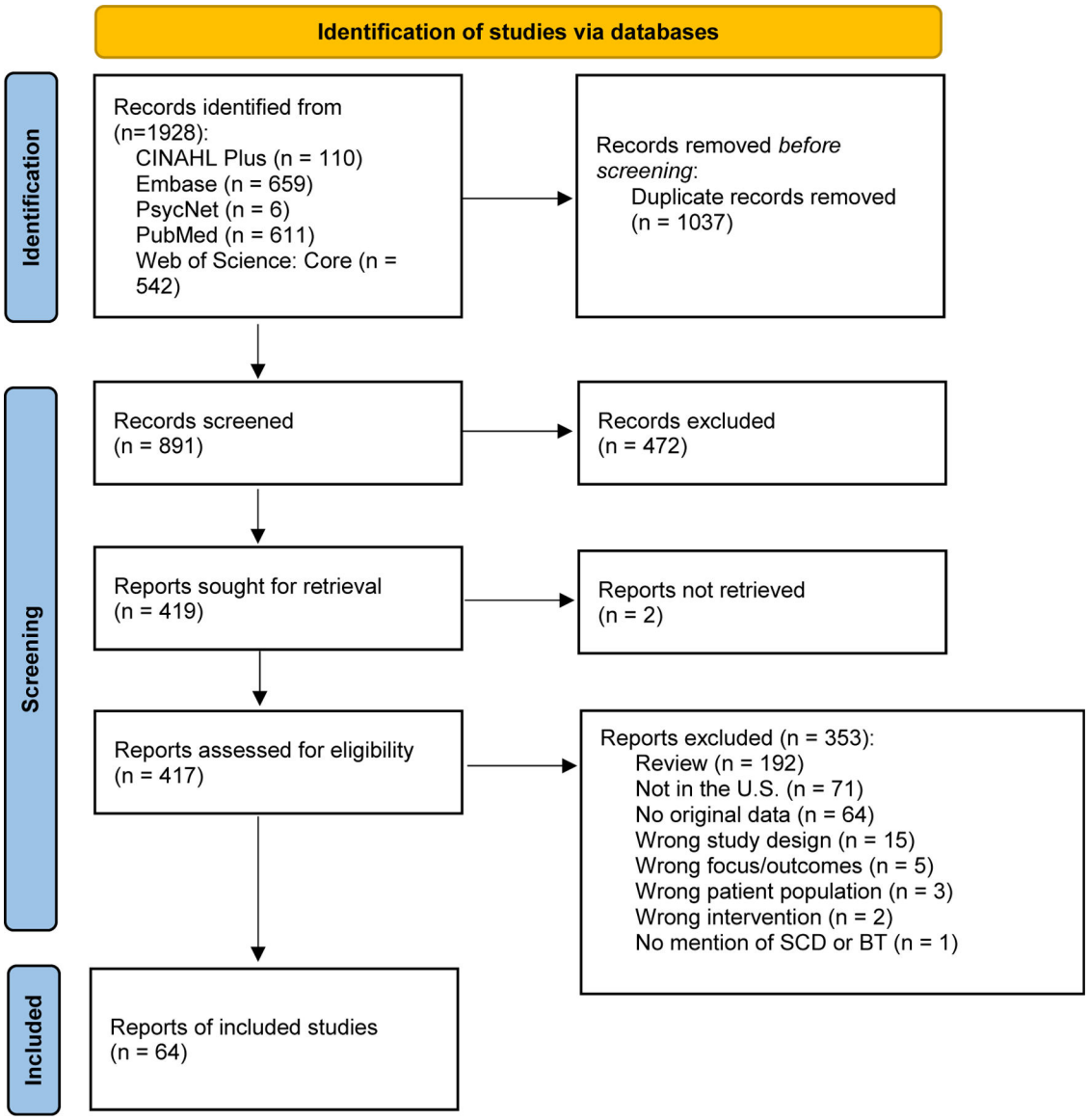


**Figure 1. PRISMA flow diagram.**

Figure 1 shows the flow of information through the scoping review. It shows the number of articles identified from the database searches and then the selection of articles after each level of screening and the final number of articles included in this scoping review. BT, beta thalassemia; SCD, sickle cell disease.

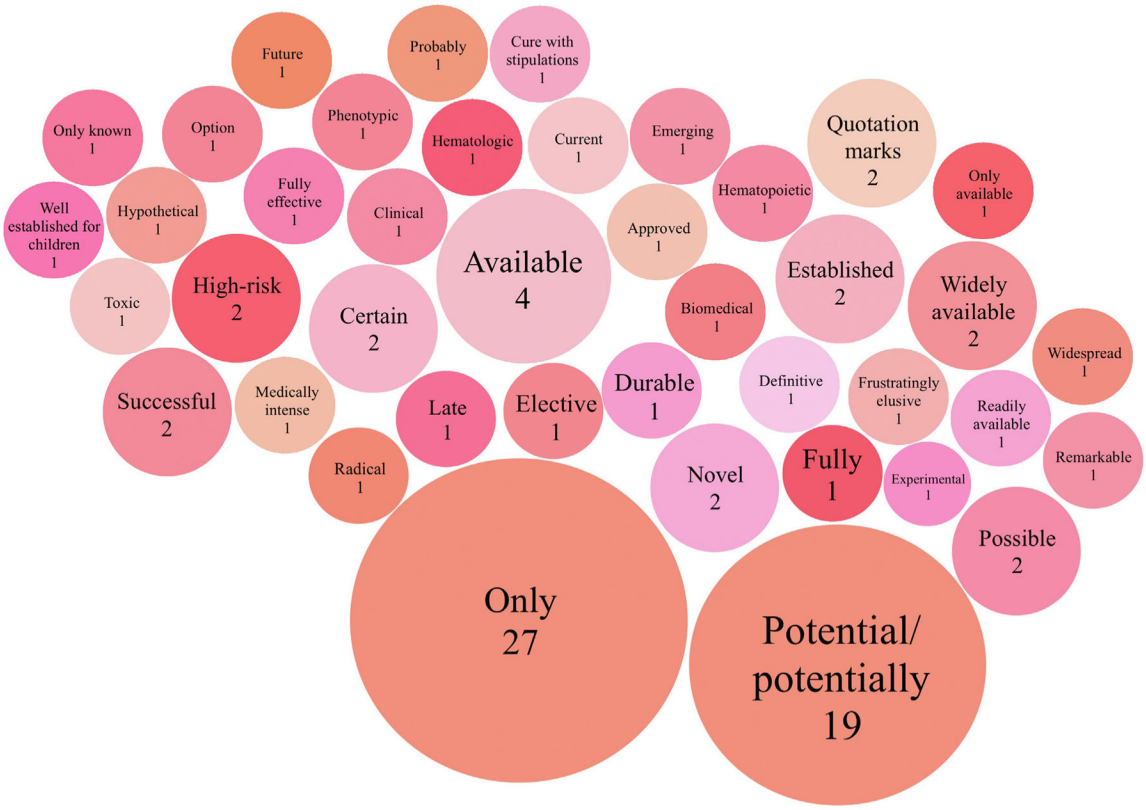


**Figure 2. Circular packing chart of cure qualifiers.**

Figure 2 depicts the frequency that a cure qualifier was used across all documents. The size of the bubble is proportional to the number of times the qualifier was used.

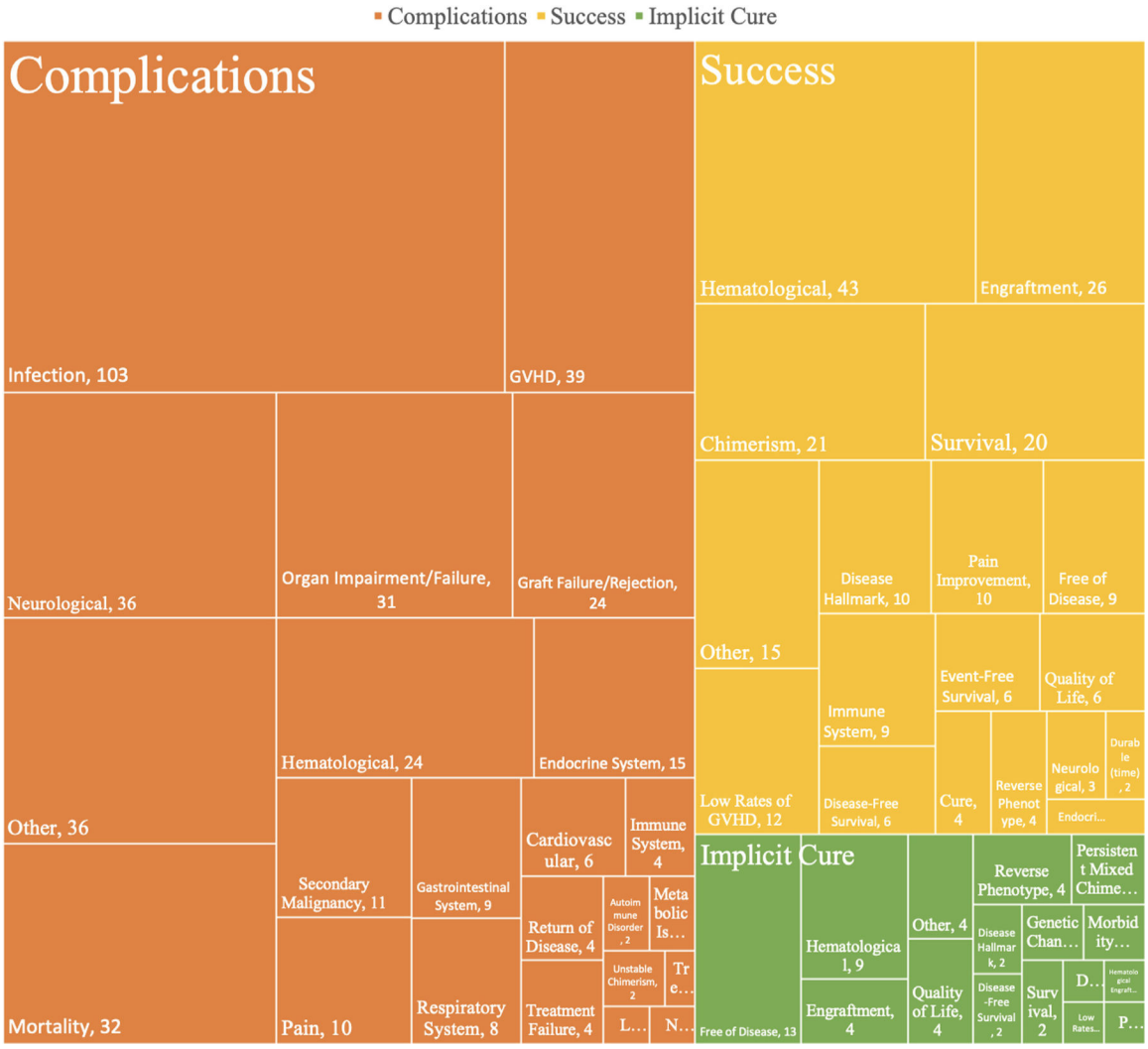


**Figure 3. TreeMap of categories of complications, success, and implicit cure.**

Figure 3 depicts a TreeMap of the various categories of complications, success, and implicit cure across all documents. The size of the box is proportional to the number of times the category was mentioned across all documents with the frequency placed next to the category.

**Table 1**

Study characteristics ($n$ = 64)

| Study Characteristics | % | Frequency |
|---|---|---|
| Decade published | | |
| 1990–1999 | 9.0 | 6 |
| 2000–2009 | 16.0 | 10 |
| 2010–2019 | 53.0 | 34 |
| 2020 to present | 22.0 | 14 |
| Location | | |
| United States Only | 73.0 | 47 |
| United States and other country | 14.0 | 9 |
| Location unclear only | 11.0 | 7 |
| United States and location unclear | 2.0 | 1 |
| Funding source | | |
| Public | 31.0 | 20 |
| Private | 13.0 | 8 |
| Public-private collaboration | 14.0 | 9 |
| Not mentioned | 42.0 | 27 |
| Intervention type | | |
| BMT/SCT[a] only | 91.0 | 58 |
| Gene therapy (GT) only | 5.0 | 3 |
| BMT/SCT/GT | 5.0 | 3 |
| Study design | | |
| Experimental only | 41.0 | 26 |
| Observational only | 38.0 | 24 |
| Qualitative only | 9.0 | 6 |
| Economic evaluation only | 3.0 | 2 |
| Experimental and observational | 3.0 | 2 |
| Observational and qualitative | 6.0 | 4 |
| Population characteristics | | |
| Illness population | | |
| Sickle cell disease (SCD) only | 72.0 | 47 |
| Beta thalassemia (BT) only | 16.0 | 10 |
| SCD and beta thalassemia | 12.0 | 7 |
| Stakeholder population | | |
| People with illness only | 78.0 | 50 |
| Family and/or caregiver | 8.0 | 5 |
| People with illness and family and/or caregiver | 15.0 | 9 |
| Age group | | |
| Pediatric only | 20.0 | 12 |
| Adult only | 23.0 | 15 |
| Pediatric and adult | 52.0 | 34 |

| Study Characteristics | % | Frequency |
|---|---|---|
| Not mentioned/unclear | 7.0 | 4 |

*BMT*, bone marrow transplantation; *BT*, beta thalassemia; *GT*, Gene therapy; *SCD*, sickle cell disease; *SCT*, stem cell transplant.

[a]Bone marrow transplant/stem cell transplant.

**Table 2**

Curative and functional language findings ($n = 64$)

| Curative and Functional Language | % | Frequency |
|---|---|---|
| Number of times a curative word was used | | |
| 1–5 | 58.0 | 37 |
| 6–10 | 17.0 | 11 |
| 11–15 | 8.0 | 5 |
| 16–20 | 8.0 | 5 |
| 21+ | 10.0 | 6 |
| Presence of explicit definition of cure (Yes) | 11.0 | 7 |
| Presence of implicit definition of cure (Yes) | 43.0 | 27 |
| Implicit/explicit cure definition domains | | |
| Physical only | 28.0 | 18 |
| Not applicable | 59.0 | 38 |
| Combination of physical, social/family well-being; emotional well-being; functional well-being; other | 14.0 | 8 |
| Mention of functional outcomes (Yes) | 34.0 | 23 |
| Functional outcome domains | | |
| Social/family, emotional, and functional well-being | 19.0 | 12 |
| Not applicable | 63.0 | 40 |
| Combination of social/family well-being; emotional well-being; functional well-being; other | 18.0 | 12 |

**Table 3**

Explicit definitions of cure

| Definition |
|---|
| "…[thalassemia-free] survival curves of these patients reached a plateau around 3 year after BMT and remained unchanged there-after…"[45] |
| a) "…capable of producing and maintaining a normal hemoglobin level in the recipient."[48] |
| b) "functional graft"[48] |
| c) "developed PMC [persistent mixed chimerism]"[48] |
| "…relief from SCD and recovery after the transplant."[7] |
| "…replaces the defective product with normal cells…"[49] |
| "…no subsequent disease-related expenditures."[47] |
| "…'fully effective' cure as one that completely suppresses disease-related complications and costs and restores life expectancy and health-related quality of life (HRQoL) to that of a comparable individual unaffected by the disease."[30] |
| "…100 percent probability of cure and 0 percent short term mortality (survival-cure)."[32] |