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# Primary caregiver decision-making in hematopoietic cell transplantation and gene therapy for sickle cell disease

**Cynthia B. Sinha**[1], **Nitya Bakshi**[1,2], **Diana Ross**[1], **George Loewenstein**[3], **Lakshmanan Krishnamurti**[1,2]

[1]Department of Pediatric Hematology-Oncology-BMT, Emory University, Atlanta, Georgia

[2]Aflac Cancer and Blood Disorders, Children's Healthcare of Atlanta, Atlanta, Georgia

[3]Department of Social and Decision Sciences, Carnegie Mellon University, Pittsburgh, Pennsylvania

## Abstract

**Background:** Improved outcomes and the availability of clinical trials of hematopoietic cell transplantation (HCT) from alternate donors and genetically modified autologous hematopoietic progenitor cells have expanded the applicability of HCT for sickle cell disease (SCD). To understand the perspective of primary caregivers exploring HCT in the current milieu, we asked the research question "What motivates primary caregivers to decide to consider HCT and to seek, and to attend, an HCT consultation?"

**Procedures:** We conducted qualitative interviews with primary caregivers within one week after a consultation for HCT for SCD. Data were analyzed using open and axial coding stages of grounded theory methodology.

**Results:** We interviewed 29 primary caregivers (26 females, age 29 to 64 [median 42] years). Primary caregivers report of SCD complications in their child included at least one in the last year by 23 (82%), few or none by 8 (28%), and pain on ≥3 days a week by 13 (46%) primary caregivers. Qualitative analysis revealed that primary caregivers, (i) learn about curative options through social networks, social media, and the news media; (ii) seek consultation because of their child's diminished quality of life, recent complications, an imminent major medical decision, or anxiety about future severe complications; and (iii) see gene therapy as a new, less invasive, and more acceptable treatment.

**Conclusion:** Primary caregivers of children with SCD learn about HCT through social networks, social and news media, and explore HCT as a means to prevent SCD complications and help their child live a normal life.



Correspondence: Lakshmanan Krishnamurti, Emory University, Atlanta, GA. lkrishn@emory.edu.

CONFLICTS OF INTEREST

There are no known conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

**Keywords**

gene therapy; hematology; hematopoietic stem cell transplantation; medical decision-making; pediatric; sickle cell disease

## 1 | INTRODUCTION

Sickle cell disease (SCD) is a genetic disorder of the red blood cell that affects approximately 100 000 individuals in the United States,[1] and is associated with vaso-occulsive episodes (VOE), acute chest syndrome, stroke, and splenic sequestration, progressive organ dysfunction, impaired quality of life, and premature mortality.[2–5] Hydroxyurea (HU), and the recently approved disease-modifying therapies, including L-glutamine,[6] voxeltor,[7] crizanlizumab,[8] offer the possibility of long-term amelioration of the disorder. Lack of access to high-quality, comprehensive care, health disparities, and other sociodemographic factors all contribute to difficulties in adherence to, and the long-term effectiveness of, these regimens.[9]

Hematopoietic stem cell transplantation (HCT) from allogeneic donors and, more recently, gene therapy (GT) with autologous genetically modified hematopoietic stem cells, offer the possibility of long-term disease amelioration. HCT/GT are associated with substantial risks of morbidity and mortality in the short term, as well as a risk of chronic, and even disabling, complications. The safety and efficacy of HCT have been improving with advances in supportive care.[10] The vast majority of patients have undergone HCT from human leukocyte antigen (HLA) identical related donors. The principal barriers to HCT are the unavailability of HLA-matched donors and the disparity between physicians' and patient or primary caregiver assessment of the patient's disease severity in the consideration for HCT.[11,12] There appears recently to be a paradigmatic shift in the application of HCT for SCD with the advent of HCT from alternate donors, and the emergence of GT. In fact, more than 65% of HCT for SCD reported to the Center for International Blood and Marrow Transplant Research (CIBMTR) from 2008 to 2017 have been performed after 2013.[13,14] This paradigmatic shift is likely reflective not only of the availability of novel treatments but also of the increased willingness of physicians and patients to consider HCT.[15,16] Previous studies have investigated attitudes in the general SCD community rather than people who are actively considering HCT.[17–20] We undertook a qualitative study to gain insight into the perspective of primary givers who attended a consultation with an HCT physician for discussing HCT options for SCD in the current era of expanded curative options. Our research question was: "What motivates primary caregivers to decide to consider HCT and to seek and to attend an HCT consultation?"

## 2 | METHODS

During 2019, we conducted qualitative interviews with primary caregivers of children with SCD attending a consultation with the same HCT physician at Children's Healthcare of Atlanta, Georgia. The program has extensive experience with performing HCTs for SCD and has an established referral pattern from the large institutional SCD program and from elsewhere. Patients attend an HCT consultation at the recommendation of their sickle cell

hematologist. All consults were accepted regardless of patient age, disease severity, the availability of a suitable donor, or eligibility for participation in a currently open clinical trial.

Because of the excellent outcomes of HCT from HLA-identical sibling, this treatment was offered for young patients with symptomatic SCD with a sibling match. Most primary caregivers with an HLA-matched sibling donor for their child were considering when, rather than whether, to proceed with HCT. Primary caregivers of patients without an HLA-matched sibling donor were willing to consider participation in clinical trials for both haploidentical donor HCT and GT.

After consultation with the HCT physician, primary caregivers were approached for consent to the study. Qualitative interviews were conducted using semi-structured interview guide with probes that were adapted to donor status. Audio recordings of the interviews were transcribed verbatim. Transcripts were coded using descriptive qualitative analysis using NVivo 12 (QSR International).

The first stage of the analysis involved open coding,[21] with the lead coder performing a line-by-line analysis of the transcripts, identifying concepts, or primary caregiver responses, related to the research question. Similar concepts were grouped into categories representing overarching patterns in the data set. The second stage of analysis, axial coding, identified relationships among the categories[22] and how the relationships address the research objective. Data saturation was reached when no new concepts, related to the research objective, emerged from the data set. Final conclusions were drawn from the most frequent and relevant responses. The coding scheme used by the primary coder (CBS) was tested by two other investigators (NB) and (DR). We achieved an intercoder agreement of greater than 90%.

Patient demographics, assessment of disease severity, and the availability of suitable donors were ascertained from primary caregivers before the beginning of the qualitative interview. Results are reported in compliance with the Consolidated Criteria for Reporting Qualitative Research.[23]

## 3 | RESULTS

We interviewed 29 adults (26 females), 27 of whom identified as African American, one as mixed race, and one as White Hispanic. Ages of the primary caregivers ranged from 29 to 64 years with a median age of 42 years. The age of the child (15 female) ranged from 14 months to 18 years (median 14 years). Twenty-three (79%) primary caregivers reported that their child had experienced an SCD-related complication in the last year. Thirteen (45%) primary caregivers reported that their child had experienced pain on three or more days a week. Eight (28%) primary caregivers believed that their child experienced overall good health with few or no SCD complications.

Primary caregivers provided patient history of SCD-related complications, current treatment plans, perception of patient's experience with SCD-related pain, and perception of the patient's overall health (Table 1).

We developed three findings from the analysis. (1) Families are learning about curative options through social networks, social media, and news media. (2) Caregivers are motivated to seek consultation because of their child's diminished quality of life, recent complications, the need to make a major medical decision, or concern about future severe complications. (3) Primary caregivers view GT as a new and potentially less invasive, lower risk, curative treatment, and associated with simpler recovery as compared with allogeneic HCT.

### 3.1 | Families are learning about curative options through social networks, social media, and news media

Primary caregivers reported learning about HCT from informal social networks and participation in groups on social media such as Facebook. They felt optimistic when they heard reports of successful HCT directly from other primary caregivers or adult patients and hoped that HCT may be a cure for SCD (Table 2).

Primary caregivers reported using social media to keep up to date on SCD treatments and participate in support groups with other primary caregivers of children with SCD. These groups appeared to provide general, but incomplete information about procedures associated with HCT and GT. For instance, most caregivers were unaware that GT involved the administration of myeloablative chemotherapy. Thirteen primary caregivers, including three parents of children with an HLA-identical sibling donor, indicated that they initiated the conversation for HCT or GT with the hematologist, who in turn referred them to the HCT physician. However, this was self-reported by the caregiver during the interview. We were unable to determine if the hematologist had brought up the possibility of HCT previously and what conversations preceded the ordering of the HLA typing of the siblings. Seven primary caregivers reported watching the show "60 Minutes" featuring a young woman who underwent GT and decided to seek a consultation to learn more about this option.

Only one family, out of the 29, indicated as a result of what they learned in the consultation that they would no longer consider HCT or GT. Caregivers who attended a consultation expressed openness to the possibility of HCT or GT even when it was not an immediately available option for their child.

### 3.2 | Caregivers are motivated to consider HCT and seek consultation because of their child's diminished quality of life, recent complications, a need to make a major medical decision, or concern about future severe complications

Primary caregivers reported feeling distressed by how SCD limited their child's full participation in age-appropriate activities. They wanted their child to be able to lead a "normal life" (Table 3).

Repeated school absences were a major cause of concern for primary caregivers. In addition to falling behind academically, they worried that repeated school absences socially isolated their child from their peers and school activities.

The majority of the children in this study reported low physical endurance, which limited their participation in activities such as sports, athletics, and dance. When asked if they believed their child could "run, jump, and play" like their peers without SCD, primary

caregivers described the limitations as well as accommodations that had to be made to allow their child to participate in activities to the best of their ability.

Chronic transfusion therapy (CTT), interfered with social activities, contributed to school absences, and may place limitations on future plans. At the time of the interview, six children were receiving CTT, five of whom were adolescents. The adolescents found the treatments to be time-consuming, contributed to increased anxiety, and limited participation in school and social activities. Three primary caregivers discussed the concern that CTT limited the choices of colleges their child could attend.

Some children experienced anxiety and depression from current SCD complications, as well as fearing future complications, such as unpredictable pain crises. Thirteen primary caregivers reported that their child experienced pain on three or more days a week and such pain episodes caused ongoing anxiety for both primary caregiver and child. Chronic and acute pain episodes frequently caused numerous ED visits, missed school, and social isolation due to long periods of recovery. Primary caregivers reported being distressed watching their child experience pain or other severe SCD complications and reported feeling helpless about not being able to help their child while children articulated becoming “tired of living like this.”

In a number of cases, a recent complication motivated primary caregivers to meet with an HCT physician to learn about curative options. Severe life-threatening complications such as a stroke or acute chest syndrome were scary as well as concerning for organ damage. Primary caregivers of children who experienced several VOEs were especially likely to seek a curative option to prevent ongoing debilitating pain. Some of the primary caregivers consulted with the HCT physician as part of exploring all of their options to prevent future complications from SCD. Primary caregivers also reported scheduling a consultation when faced with a medical recommendation for chronic transfusion due to a transcranial Doppler indicating risk for stroke, splenectomy for severe or recurrent episodes of splenic sequestration, or surgery for avascular necrosis of the hip.

Eight primary caregivers reported that their child had not experienced a serious SCD-related complication in the last year and, in fact, believed their child to be in overall good health. They were motivated to meet with the HCT physician because of fear of the unpredictable progression of SCD. They likely learned, through the internet and social media, of the potential for their child to experience severe SCD-related complications and premature mortality. A few primary caregivers reported that they had a close friend or family member who had SCD, and had learned firsthand about the debilitating experience of living with SCD. Fear of future complications and the anxiety that their child may not be able to cope in adulthood motivated primary caregivers to attend the consultation.

### 3.3 | Primary caregivers view GT as a new and potentially less invasive, lower risk, curative treatment, and one that is associated with simpler recovery as compared with allogeneic HCT

Primary caregivers whose children did not have an HLA-identical sibling match or had previously been to a consultation for HCT specifically requested a referral to schedule a

consultation to learn more about GT (Table 4). Primary caregivers came to the consultation believing GT is a “cure” for SCD. Those who had attended a consultation previously were aware that HCT involved chemotherapy and were concerned about both the short-term toxicity of chemotherapy and the potential for long-term side effects, such as infertility and subsequent malignancy. Primary caregivers were unaware that GT also involves chemotherapy. Nonetheless, they believed autologous GT may be less invasive, involved less risk, and that the recovery would be simpler than allogeneic HCT.

In each consultation, the physician discussed all HCT and donor options, including HLA-matched siblings, alternate donor HCT, and GT. Primary caregivers learned about clinical trials for gene addition, gene editing, and the use of lentiviral vectors and other methodologies involved in GT and early results on the outcomes of different clinical trials. Many primary caregivers were not aware of clinical trials for haploidentical donor HCT. However, after hearing about the relative risks and outcomes with various types of HCT, many primary caregivers expressed a preference for pursuing GT.

Primary caregivers were unaware of current clinical trials prior to the consultation. After the consultation, all of the primary caregivers in this study expressed willingness for their child to participate in a clinical trial, and several were disappointed when they learned that their child may not currently qualify for a clinical trial. At the time of this study, very few children met the eligibility criteria for GT clinical trials but were eligible for haploidentical donor HCT. Five primary caregivers stated their preference to wait until their child met eligibility criteria for GT clinical trials.

## 4 | DISCUSSION

To the best of our knowledge, this study is the first to evaluate primary caregivers’ perspective in an era of rapid expansion of HCT options focusing on primary caregivers’ motivation for considering HCT and consulting with an HCT physician. The study is unique in that it describes the perspective of families who attended an HCT consultation in real life rather than sampling attitudes in hypothetical situations in the general SCD community who may or may not be facing a similar set of circumstances.[17–19] Stigglebout et al.[24] describe a framework to understand the differences between how real-life health states and imagined health utilities might impact the stimulus, interpretation, judgment, and response phases of decision-making. Ultimately, achieving an understanding of decision-making may require an integration of primary caregiver perspectives exploring both the real and imagined health utilities in the affected population.

Families with no HLA-matched donor attended the consultation to learn if they had any curative options at all. These families were also more likely to have some awareness of GT and specifically requested more information on this treatment. We are unable to verify if the motivation to attend the consultation differed by donor status as all of the families who actually attended the consultation were motivated to learn if there was a “cure” option for their child. However, the content of the consultation differed depending on donor status. The families of patients with an HLA-identical sibling match had more in-depth dicussion on the timing for pursuing HCT.

An intriguing observation was how a recent severe disease complication or the urgency imposed by the need for a medical decision triggered a consultation regarding HCT. Loewenstein[25] postulated a hot-to-cold empathy gap[25] to describe how when people are in a cold state, they underestimate the influence of a “hot”, visceral state, e.g., being angry, in pain, or hungry on their behavior or preferences. In medical decision-making, for instance, a hot-to-cold empathy gap may explain treatment choices when cancer patients are asked to choose between treatment options right after being told about their diagnosis. Most of the primary caregivers in this study met with the HCT physician following recent SCD-related complications or observation of diminished quality of life. Thus, the concept of the hot-cold empathy gap explains why caregivers may seek a consultation for HCT soon after a life-threatening event. In the absence of an affective state, primary caregivers may not feel an urgent need for medical decision-making for their child. Some primary caregivers who acknowledged that their child was currently experiencing overall good health considered the potential for future complications even when not experiencing them in the present. Through social networks that included adults with severe disease, these families became very concerned about the imminence of disease progression. Both scenarios prompted primary caregivers to meet with the physician to learn about their options. In fact, some primary caregivers in the latter scenario were dismayed to learn their child did not qualify for a current clinical trial because their child was not “sick enough”.

With the increase in the number of successful HCT for SCD, it is likely that families will come across, on social networks, more individuals with a positive experience of HCT. These networks may play an influential role in their consideration of curative treatments.[26]

Raising a child with SCD is associated with a myriad of psychological stressors for primary caregivers.[27] Families experience stress from the burden of SCD treatments, such as CTT, regular clinic visits, and the financial hardship from missed workdays.[27,28] Taking care of their child through the pain crises and other severe SCD-related complications may cause the greatest distress for primary caregivers.[27] Primary caregivers cope in a variety of ways, such as joining support groups as well as engaging in health information–seeking behavior (HISB).[29] Primary caregivers feel powerless watching their child’s pain and suffering from SCD, and seeking information about a “cure” for SCD may assist in coping with their child’s disease. When individuals indulging in HISB find the information they seek, they may experience improved psychological adjustment to illness.[29] Similar to the hot-cold empathy gap,[25] Lambert et al.[29] describe the antecedent gap where, after experiencing a severe complication or receiving a dire diagnosis, there may be a gap between what health information the primary caregivers have and what they want to know. Although after the consultation, most primary caregivers felt that they had received an overwhelming amount of information to consider and had a lot to think about and discuss with their family, they also perceived that they now had “options” for their child with SCD.

Prior to the consultation, most primary caregivers were not aware of haploidentical donor option, but had heard about GT, and many had scheduled the consultation to learn specifically about GT. Primary caregivers believed GT to be “less invasive” than HCT because autologous HCT is not associated with GVHD. However, most primary caregivers expressed more concern about the short- and long-term effects of chemotherapy than

concerns for GVHD. The discussion of GT revealed a willingness to participate in an early-phase clinical trial. Our study confirms observations in the general SCD community for the consideration of GT.[30–32] Historically, African Americans have been reported to have a distrust of the medical community in general, and clinical trials, in particular.[33] Haywood et al.[34] report changing attitudes among SCD patients about participation in clinical trials. In their study, more education, better-perceived health status, and previous clinical trial participation were all associated with more positive attitudes about clinical trials.[34]

We have previously reported that an interplay of patient-related and disease-related factors, decision type, and physician-related factors, as well as institutional frameworks, influenced physician perspectives on treatment options and decision-making regarding these therapies.[35] Ready access to a well-established comprehensive SCD program with many open clinical trials, and an HCT center with experience in SCD, may have influenced the willingness of primary caregivers in this study to consider participation in clinical trials.

This study has several limitations. These were observations in an institution following more than 2000 patients with SCD, with an established referral pattern to a large HCT program with experience in SCD and several open clinical trials for HCT/GT for SCD. The threshold for consultation may be low because all consults were accepted regardless of age, disease severity, availability of a suitable donor, or eligibility for a currently open study. Thus, the perspective of primary caregivers seen in consultation at this center may not be generalizable. This study may however be descriptive of the perspective of primary caregivers, absent the individual, physician, and institutional barriers to the consideration of HCT/GT.[35] We were able to enroll 29 primary caregivers who attended HCT consultation in the year 2019, which coincided with highly publicized reports in the media of early cases of GT. The perspective of the primary caregivers reflects the prevalent attitudes in this period. This study did not capture the perspective of those primary caregivers who were offered a consultation, but either refused or did not keep the appointment because of ambivalence of HCT or another reason.

## 5 | CONCLUSION

Concern about diminishing quality of life, a hope for their child to have a more “normal” life, recent severe SCD-related complications, and the need to make a major medical decision motivated primary caregivers to consider HCT. Gathering information from social media and social networks, many primary caregivers sought to learn more about GT which they viewed as a new and potentially less risk treatment option. These findings provide a framework for understanding how primary caregivers approach the decision to consider HCT/GT and to seek HCT consultation. The evident interest in learning about HCT/GT options provides the rationale for incorporating the discussion of curative options with families into comprehensive care.

## DISCLOSURES

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## Abbreviations:

| | |
|---|---|
| **CIBMTR** | Center for International Blood and Marrow Transplant Research |
| **CTT** | chronic transfusion therapy |
| **GT** | gene therapy |
| **GVHD** | graft versus host disease |
| **HCT** | hematopoietic stem cell transplantation |
| **HISB** | health information-seeking behavior |
| **HLA** | human leukocyte antigen |
| **HU** | hydroxyurea |
| **SCD** | sickle cell disease |
| **VOE** | vaso-occulsive episodes |

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**TABLE 1**

Patient characteristics as reported by their primary caregivers

| | Patient characteristics as reported by their primary caregivers | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Primary caregivers believe their child is not in good overall health due to SCD. *n* = 21 | | | | | Primary caregivers their believe child is in good health despite SCD. *n* = 8 | | | |
| | Chronic pain | Stroke | Chronic transfusion therapy | Taking hydroxyurea | HLA-identical sibling match | Chronic pain | Chronic transfusion therapy | Taking hydroxyurea | HLA-identical sibling match |
| HbSS | 17 | 2 | 1 | 17 | 4 | 0 | 5 | 2 | 3 |
| HbSß | 2 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| HbSC | 2 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |

**TABLE 2**

Families are learning about curative options through social networks, social media, and news media

| Subthemes | Quotes |
|---|---|
| Learning through community and social networks | "We just found a family member in church who just went through it [HCT] last year. The child is doing very well." |
| Interaction with support groups on social media | "I am in the BMT group and the sickle cell group. I have been reading and seeing what is going on. Doing my own research on it. I feel in my heart that I should do this for her." "I had heard about it [HCT]. I am part of a Facebook sickle united support group. I learned about it through there." |
| Parent initiated internet research | "I knew that it [HCT] was the only cure. That's what I researched online. That's what I thought." |
| Stories on news media | "About a month or two ago there was the CBS documentary about sickle cell about the gene transplant [sic]. I told her [daughter] to go listen." "And then, of course you know, the 60 Minute story [about gene therapy] came out." |

**TABLE 3**

Caregivers are motivated to consider HCT and seek consultation because of their child's diminished quality of life, recent complications, a need to make a major medical decision, or the concern about future severe complications

| Subthemes | Quotes |
|---|---|
| Disease is impairing the quality of life | "She would like to proceed with the gene therapy due to the fact she doesn't want to continue life having to be on the schedule with the infusions." |
| SCD complications limiting future aspirations | "I just see her wanting to do things in life, like go off to college and stuff, and I'm just kind of wary about sending her away. Knowing how many times she's sick out of the week. I just hate to see her go and not be successful because of her illness." |
| The desire to live without the fear of unpredictable complications | "It (HCT) will give you the opportunity to live life with minimum amount of risk. We may have hypertension, but we don't think that if I might go to bed today and not wake up because of the disease I have." |
| A major medical decision-making brings urgency to the disease | "I am still really concerned because she is scheduled for surgery this Friday. I still have up until that day. I still have to really make a conscious choice to whether or not removing her spleen is the best choice or keeping heron the chronic transfusion would be better because it works." |
| Recent disease complication serves as a reminder of the suffering and danger associated with the disease | "He's able to walk on his own but he has pain or you know that sound the body can make when you're walking like a cracking sound a popping sound will come upon him and he has to stop. He'll stumble. He stumbles a lot."<br>"[Child] be okay, and then all of the sudden we have an acute chest syndrome. It scared me. It [death] could just happen like that for her." |

**TABLE 4**

Primary caregivers view GT as a new and potentially less invasive, lower risk, curative treatment, and one that is associated with simpler recovery as copared with allogeneic HCT

| Subtheme | Quotes |
|---|---|
| Gene therapy is a cure for SCD | “Several success stories in my research that they are doing fine. They are doing fine. Within a year of having this gene therapy, there is literally no sickled blood cells to be found.” |
| Less invasive treatment with faster recovery than allogeneic HCT | “It is definitely is a win/win situation for anybody considering it. It [gene therapy] is not as invasive [as HCT].”<br>“The fact that it doesn’t have that long of a recovery as the BMT. I think that stuck out.”<br>“I just felt like it was a simpler process from my understanding.” |
| Less risk with no risk of GVHD | “From my understanding, they are all similar, but the risk factors seem to be a lot less with gene therapy, which is slightly more assuring.”<br>“The risk of [GVHD] is higher when you are doing the bone marrow from the donor versus him receiving his own stem cells back. So, that’s kind of the piece for me that is a game changer.” |