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Report

# Late Effects Screening Guidelines after Hematopoietic Cell Transplantation (HCT) for Hemoglobinopathy: Consensus Statement from the Second Pediatric Blood and Marrow Transplant Consortium International Conference on Late Effects after Pediatric HCT

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A B S T R A C T

Allogeneic hematopoietic cell transplantation (HCT) can halt organ damage and eliminate symptoms in hemoglobin disorders, including sickle cell disease (SCD) and thalassemia major. Managing the residual manifestations of pre-HCT disease complications and the long-term effects of HCT requires systematic monitoring, follow-up and intervention when indicated. Late complications vary with age and disease status at HCT and with transplant variables such as preparative regimen, donor source and compatibility, and immune reconstitution. An international consensus conference sponsored by the Pediatric Blood and Marrow Transplant Consortium in May 2016 entitled "Late Effects Screening and Recommendations Following HCT for Immune Deficiency and Nonmalignant Hematologic Disorders" focused on follow-up after HCT for hemoglobinopathy. An earlier publication from experts who participated in this session described the pathophysiology and spectrum of complications that HCT recipients experience after HCT for SCD and thalassemia major. This companion publication summarizes the consensus reached by this group of experts about long-term follow-up guidelines after HCT for hemoglobinopathy. In addition, these guidelines might also be included in studies of novel curative therapies such as autologous HCT after hematopoietic progenitor stem cell gene modification.



## INTRODUCTION

Hematopoietic cell transplantation (HCT) is indicated for symptomatic hemoglobinopathy and can provide a cure. The most common hemoglobin disorders treated by HCT are transfusion-dependent thalassemia major and sickle cell disease (SCD). The number of patients, predominantly children, undergoing HCT for hemoglobinopathy is increasing each year and has a worldwide distribution. This has resulted in an expanding number of HCT survivors cured of their disease with an extended number of years of life without symptoms gained after the transplant intervention, in most cases. These patients should have optimized long-term healthcare

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monitoring to ensure post-transplant well-being, so that late complications can be recognized promptly and treated or supported early.

A conference sponsored by the Pediatric Blood and Marrow Transplant Consortium in May 2016 focused on long-term follow-up after HCT in nonmalignant disorders and included a session for hemoglobinopathies [1]. The key aims of this meeting of international experts in the field were to summarize current knowledge regarding late effects and disease-related outcomes after HCT for hemoglobinopathies, identify gaps in uniformity of long-term follow-up after transplant, describe areas of future research, and develop guidelines to aid in standardized screening and monitoring after HCT. In a previous publication this group reviewed existing data on survival and follow-up after HCT for hemoglobinopathies [2]. In this article we summarize our recommendations about monitoring after HCT and provide roadmaps for longitudinal evaluation based on unique disease- and transplant-related features. The goal is to focus on conducting comprehensive follow-up after HCT, highlighted by medical need and by areas for improvement, thus promoting new investigation in this field. Further, these recommendations can be adapted for future transplant and gene modification trials, follow-up protocols, or long-term registries as appropriate and can be used as standard medical care by providers and in survivorship programs.

Late effects after HCT are influenced by recipient age at transplant, disease status and pre-existing comorbidities, transplant method and conditioning regimen, donor source, HLA compatibility, post- transplant complications, and immune reconstitution. Avoidance of complications and mortality caused by the underlying disease or the transplant itself requires anticipation, early recognition, and adequate medical support [3-5]. There are also focus points of risk to recognize and mitigate when designing a clinical trial for these disorders.

Based on current knowledge about long-term follow-up in hemoglobinopathy patients, the areas benefitted by systematic follow-up after HCT and have research value include the following:

- Defining transplant outcomes in relation to recipient age, disease status, donor sources, and transplant methods to identify areas for improvement
- Tracking engraftment to ensure stable mixed or full donor chimerism
- Minimizing transplant-related complications such as mortality, graft-versus-host disease, (GVHD), and delayed immune reconstitution
- Defining strategies to evaluate and reduce iron overload
- Organ function monitoring, including cardiopulmonary, liver, and kidney functions
- Monitoring central nervous system (CNS) outcomes and neurocognitive function after posterior reversible encephalopathy syndrome episodes, cerebral vasculopathy including moyamoya disease, cerebral atrophy, and hemorrhagic or ischemic lesions in the brain
- Endocrine organ function monitoring of thyroid and gonadal function, linked to growth and pubertal development/fertility
- Assessment of pain and pain control post-HCT including opioid use
- Quality of life assessment, education, employment
- Healthcare utilization before, during, and after HCT

These surveillance guidelines take into consideration the prioritized factors, listed above, that determine the success of HCT as a curative intervention.

Donor characteristics also might affect follow-up planning after HCT for hemoglobinopathies. These considerations include not only the source of donor cells but also other genetic characteristics. For example, if a donor had thalassemia or sickle trait, recipient follow-up should consider trait modifiers. If the donor had glucose-6-phosphate dehydrogenase enzyme deficiency, the recipient might benefit from counseling about this condition. However, neither condition is a contraindication to stem cell donation in a patient with hemoglobinopathy [6,7].

## FOLLOW-UP RECOMMENDATIONS AFTER HCT FOR THALASSEMIA

After HCT for transfusion-dependent thalassemia, there is a risk of chronic anemia in the absence of optimal management, complications of iron overload and its treatment, and RBC allo-immunization [8]. Transfusion-related infections have declined after adopting modern blood screening procedures, especially in developed countries. Monitoring and management guidelines post-HCT should take into consideration organ toxicities associated with transfusions and iron overload such as cardiac, hepatic, and endocrine insufficiency [9-12]. Many manifestations of endocrine function impairment are multifactorial; iron toxicity, chelation medication toxicity, and HCT regimens are contributing factors. Impaired glucose tolerance post-transplant in nonmalignant disorders is rare and was previously a consequence of unfractionated radiation-based conditioning regimens. Hepatitis C virus (HCV) infection was common in thalassemia patients, particularly in those transfused before second-generation ELISA tests for detecting HCV in donors became available [13]. The risks of chronic HCV infection persists in patients with viremia and should be treated with modern antiviral therapy [14,15]. Splenectomized patients will remain vulnerable to encapsulated bacterial organisms lifelong.

Conditioning regimens with iron overload together may increase susceptibility to post-transplant hepatic sinusoidal obstruction syndrome early or late onset after HCT. Cardiac function generally stabilizes after HCT and may improve after reducing the cardiac iron burden [16]. Complications related to iron overload can be effectively prevented post-HCT with appropriate iron reduction therapy (regular phlebotomy or iron chelation therapy) and is expected to improve in about 50% of patients depending on age and compliance. Hypogonadism is the most frequent endocrine complication described; the 2 major risk factors for hypogonadism are iron overload and conditioning regimens that contain busulfan or treosulfan. In this setting the incidence of hypogonadism after HCT before puberty is high (Supplemental Table S1). Approximately 40% of children will experience puberty normally after HCT despite having clinical and hormonal evidence of hypogonadism [17]. Fertility, however, is better preserved when HCT is performed in young, prepubertal children, presumably because of the gonadal dormancy and the shorter duration of exposure to iron overload [18]. The development of reduced-toxicity/reduced-intensity regimens might also attenuate the risk of gonadal damage [19,20]. Table 1 illustrates details on thalassemia-specific complications and the long-term follow-up schedule recommended for identification of complications and intervention. Although no pregnancy-related complications have been reported to date, careful follow-up is nevertheless recommended during

**Table 1**
Follow-Up Recommendations after HCT for Thalassemia and SCD

| Organ/System | Thalassemia | SCD |
|---|---|---|
| Immune functions<br>-Lymphocyte subpopulations<br>-Lymphocyte proliferation<br>-Immunoglobulin levels<br>-Vaccine-specific antibody titers | • Monitor at 6 months, 1 year, then every 6 months until immune recovery is complete; include post-vaccination-specific antibody titers (tetanus, diphtheria, pneumococcus)<br>• Immunizations per ASBMT/EBMT guidelines (http://www.nature.com/bmt/journal/v44/n8/full/bmt2009263a.html?foxtrotcallback=true)<br>• Consider antibiotic prophylaxis against encapsulated organisms until B cell recovery and indefinitely in post-splenectomy patients<br>• Pneumocystis *jirovecii* prophylaxis for 6 months and until systemic immunosuppression is on a wean in the absence of cGVHD<br>• Give fungal prophylaxis until 100 days after HCT; extend prophylaxis if there is active cGVHD treated by immunosuppression | • Monitor at 6 months, 1 year, then every 6 months until immune recovery is complete; include post-vaccination-specific antibody titers (tetanus, diphtheria, pneumococcus)<br>• Immunizations per ASBMT/EBMT guidelines (http://www.nature.com/bmt/journal/v44/n8/full/bmt2009263a.html?foxtrotcallback=true)<br>• Continue PCN prophylaxis until splenic regeneration has been proved by liver-spleen scan and a normal pitted RBC score (<1.5%) and vaccination against pneumococcus is effectively completed.<br>• Antibiotic prophylaxis against encapsulated organisms until B cell recovery and indefinitely in postsplenectomy patients<br>• Pneumocystis *jirovecii* prophylaxis for 6 months and until systemic immunosuppression is on a wean in the absence of cGVHD<br>• Give fungal prophylaxis until 100 days after HCT; extend prophylaxis if there is active cGVHD treated by immunosuppression |
| Iron overload | • Assess iron load with serum ferritin and transferrin saturation every 3-6 months commencing 6 months after HCT* until normal<br>• If abnormal, start iron depletion with phlebotomy or iron chelation ideally after stopping or reducing systemic immunosuppression. Discontinue iron reduction therapy when iron stores (serum ferritin and transferrin saturation) are in the normal range<br>• Avoid concomitant use of deferasirox and calcineurin inhibitors due to risk of nephrotoxicity<br>• Compare T2* MRI at 1 year with pre-HCT evaluation to document stability/improvement<br>• If T2* MRI is abnormal continue iron depletion or chelation until normalized | • Assess iron load with serum ferritin and transferrin saturation every 3-6 months commencing 6 months after HCT* until normal<br>• If consistently abnormal, start iron depletion with phlebotomy or iron chelation ideally after stopping or reducing systemic immunosuppression. Discontinue iron reduction therapy when iron stores (serum ferritin and transferrin saturation) are in the normal range<br>• Avoid concomitant use of deferasirox and calcineurin inhibitors due to risk of nephrotoxicity<br>• If T2* MRI is abnormal continue iron depletion or chelation until normalized |
| Heart | • Consider cardiac iron by T2* MRI at 1 year after HCT in patients with moderate or severe iron overload before HCT<br>• Echocardiogram annually for 5 years after HCT or longer if indicated<br>• If T2* value is 10-20 ms (moderate iron overload) continue standard chelation/phlebotomy until normalized<br>• If T2* < 10 ms (severe iron overload) commence intensive parenteral iron chelation therapy with continuous i.v. desferrioxamine until T2* > 20 ms<br>• Consider lipid profile at 1 year, continue annually for 5 years or as clinically indicated<br>• Monitor blood pressure annually | • Consider cardiac iron by T2* MRI at 1 year after HCT in patients with moderate or severe iron overload at HCT<br>• Echocardiogram annually for 5 years after HCT or longer if indicated<br>• If T2* value is 10-20 ms (moderate iron overload) continue standard chelation/phlebotomy until normalized<br>• If T2* < 10 ms (severe iron overload) commence intensive parenteral iron chelation therapy with continuous i.v. desferrioxamine until T2* > 20 ms<br>• Consider lipid profile at 1 year, continue annually for 5 years or as clinically indicated<br>• Monitor blood pressure annually |
| Liver | • Assess liver function tests every month through 1 year after HCT, every 3 months in year 2, and then as clinically indicated (such as cGVHD or hepatitis). Include albumin, GGT, and PT evaluation. Include ammonia level if indicated.<br>• Consider liver biopsy at 2 years after transplantation in patients who had bridging fibrosis before transplantation<br>• Consider liver biopsy at 2 years for patients who had hepatitis B (HBAg positive) or HCV before transplantation<br>• Refer patients who have HCV/hepatitis B infection to gastroenterologist/infectious disease specialist for consideration of antiviral therapy | • Assess liver function tests every month through 1 year after HCT, every 3 months in year 2, and then as clinically indicated (such as cGVHD or hepatitis). Include albumin, GGT, and PT evaluation. Include ammonia level if indicated.<br>• Consider liver biopsy at 2 years after transplantation in patients who had bridging fibrosis before transplantation<br>• Consider liver biopsy at 2 years for patients who had hepatitis B (HBAg positive) or HCV before transplantation<br>• Refer patients who have HCV/hepatitis B HB infection to gastroenterologist/infectious disease specialist for consideration of antiviral therapy |
| Lung | • Evaluate PFTs at 3, 6, and 12 months and then yearly for 2 years (TLC, $FEV_1$, FVC, $DL_{CO}$).<br>• Consider annual PFTs for patients with early compromise or if cGVHD until immunosuppressive medications have been stopped<br>• Patients with new-onset or worsening PFTs should be referred to a pulmonologist<br>• Consider echocardiography with evaluation of tricuspid regurgitation jet velocity to rule out pulmonary hypertension at 1 year, then as clinically indicated<br>• Measure pulmonary arterial pressure if tricuspid regurgitation jet velocity > 3 m/s to confirm pulmonary hypertension<br>• Patients with pulmonary hypertension should be referred to a pulmonologist | • Evaluate PFTs at 3, 6, and 12 months and then yearly for 2 years (TLC, $FEV_1$, FVC, $DL_{CO}$).<br>• Consider annual PFTs for patients with early compromise or if cGVHD until immunosuppressive medications have been stopped<br>• Patients with new-onset or worsening PFTs should be referred to a pulmonologist<br>• Consider echocardiography with evaluation of tricuspid regurgitation jet velocity to rule out pulmonary hypertension at 1 year, then as clinically indicated<br>• Measure pulmonary arterial pressure if tricuspid regurgitation jet velocity > 3 m/s to confirm pulmonary hypertension<br>• Patients with pulmonary hypertension should be referred to a pulmonologist |

(*Continued on next page*)

**Table 1**
(*continued*)

| Organ/System | Thalassemia | SCD |
|---|---|---|
| Nervous system | • Continue anticonvulsant therapy as needed if risk factors—hypertension, calcineurin inhibitors<br>• MRI of the brain at 1-2 years post-transplant in patients with CNS disease pretransplant and then as clinically indicated for patients who had neurotoxicity (PRES or non-PRES brain lesions).<br>• Refer patients if continued neurotoxicity and seizure disorder to neurologist<br>• Consider age-appropriate neurocognitive evaluation at 1 year and continue every 2 years | • Continue anticonvulsant therapy as needed if risk factors—hypertension, calcineurin inhibitors<br>• Consider brain MRA/MRI at 1 and 2 years after HCT and then every 2 years as clinically indicated in patients with a history of stroke or moyamoya pretransplant.<br>• MRI at 1-2 years post-transplant in patients with PRES or other neurotoxicity during transplant<br>• Consider age-appropriate neurocognitive evaluation at 1 year and continue every 2 years if neurotoxicity a complication<br>• Refer patients if continued neurotoxicity and seizure disorder to neurologist |
| Renal | • Monitor renal function until patient off calcineurin inhibitor or other nephrotoxic treatment and yearly for 2 years (BUN, creatinine, electrolytes, GFR or 24-hour creatinine clearance)<br>• Consider urine analysis for cells and proteinuria and renal ultrasound at 1 year, then as clinically indicated | • Monitor renal function until calcineurin inhibitor and other nephrotoxic therapy is discontinued and yearly for 2 years (BUN, creatinine, electrolytes, GFR or 24-hour creatinine clearance)<br>• Consider urinalysis for cells and proteinuria and renal ultrasound at 1 year, then as clinically indicated<br>• Consider microalbuminuria testing annually after HCT for 2 years<br>• Monitor blood pressure annually |
| Gastrointestinal | • Consider gastroduodenoscopy or colonoscopy in patients with unexplained diarrhea, malabsorption, or weight loss to evaluate for cGVHD | • Consider gastroduodenoscopy or colonoscopy in patients with unexplained diarrhea, malabsorption ,or weight loss to evaluate for cGVHD |
| Ophthalmology | • Consider evaluations at 1 year and 2 years, then as needed | • Consider evaluations at 1 year and 2 years, then as needed |
| Audiology<br>Dental | • Yearly retinal exam in patients receiving iron chelation therapy | • Yearly retinal exam in patients receiving iron chelation therapy or if sickle retinopathy |
| Thyroid | • Thyroid function tests (TSH, free $T_4$) at 6 months, 1 year, then annually through 5 years<br>• Refer patients with abnormal thyroid tests to endocrinologist for treatment | • Consider thyroid function tests (TSH, free $T_4$) at 6 months, 1 year, then yearly<br>• Refer patients with abnormal thyroid tests to endocrinologist for treatment |
| Diabetes mellitus | • Consider fasting glucose and GTT at the 1-year follow-up if there is significant iron overload or after steroid therapy is discontinued if applicable; continue as indicated | • Consider fasting glucose and GTT at the 1-year follow-up if there is significant iron overload or after steroid therapy is discontinued if applicable; continue as indicated |
| Gonads | • Yearly physical examination; track Tanner progression; gonadal hormones and gonadotropin levels when age appropriate<br>• Total and free testosterone, LH, and FSH in males ≥ 11 years of age, yearly for 2 years, then as clinically indicated if puberty delayed.<br>• Consider age-appropriate sperm analysis in male patients<br>• LH, FSH, anti-Mullerian hormone, and estradiol in female patients ≥ 11 years of age, at 1 and 2 years post-HCT, then as clinically indicated if puberty delayed<br>• Refer patients with evidence of pubertal delay, low testosterone levels, or females with primary or secondary amenorrhea to endocrinologist, gynecologist, or andrologist for hormonal treatment<br>• Counsel regarding genetic transmission of disease | • Yearly physical examination; track Tanner progression; gonadal hormones when age appropriate<br>• Consider total and free testosterone, LH, and FSH in males ≥ 11 years of age, yearly for 2 years, then as clinically indicated if puberty delayed.<br>• Consider age-appropriate sperm analysis in male patients<br>• Consider LH, FSH, anti-Mullerian hormone, and estradiol in female patients ≥ 11 years of age, at 1 and 2 years post-HCT, then as clinically indicated<br>• Refer patients with evidence of pubertal delay, low testosterone levels or females with primary or secondary amenorrhea to endocrinologist, gynecologist, or andrologist for hormonal treatment<br>• Counsel regarding genetic transmission of disease |
| Growth | • Evaluate height, weight, and body mass index at 6 months and then yearly<br>• Monitor every 6 months if growth velocity plateaus so intervention can be planned as needed<br>• Assess hormone levels for short stature (IGF-1, IGF-BP3) and bone age if within growth period by age<br>• Refer patients with growth retardation to endocrinologist to discuss growth hormone treatment | • Evaluate height, weight, and body mass index at 6 months, and then yearly<br>• Monitor every 6 months if growth velocity plateaus so intervention can be planned as needed<br>• Assess hormone levels for short stature (IGF-1, IGF-BP3) and bone age if within growth period by age<br>• Refer patients with growth retardation to endocrinologist to discuss growth hormone treatment |
| Bone health | • Vitamin D (25-OH) level and bone mineral density evaluation for all patients at 1 year after HCT and subsequently as indicated<br>• Patients with osteopenia and/or osteoporosis should receive vitamin D and calcium supplementation<br>• Consider MRI of the joints to evaluate for avascular necrosis in symptomatic patients on steroid therapy (cGVHD)<br>• Consider referral to endocrine services for patients with osteoporosis | • Vitamin D (25-OH) level and bone mineral density evaluation for all patients at 1 year after HCT and subsequently as indicated<br>• Patients with osteopenia and/or osteoporosis should receive vitamin D and calcium supplementation<br>• Consider MRI of the joints to evaluate for avascular necrosis in symptomatic patients on steroid therapy (cGVHD)<br>• Consider referral to endocrine services for patients with osteoporosis |
| Spleen function | | • Consider liver spleen scan and/or pitted RBC count |
| Engraftment/ chimerism | • If full donor chimerism present at 100 days, evaluate yearly for 2 years.<br>• If chimerism is mixed, consider evaluation every 3-6 months for 2 years; if stable, yearly thereafter<br>• Evaluation of myeloid chimerism preferable if available<br>• Can monitor hemoglobin level in lieu of chimerism and evaluate chimerism if microcytic anemia | • If full donor chimerism present at 100 days, evaluate yearly for 2 years.<br>• If chimerism is mixed, consider evaluation every 3-6 months for 2 years; if stable, yearly thereafter<br>• Evaluation of myeloid chimerism preferable if available<br>• Consider hemoglobin electrophoresis evaluation yearly if chimerism stable |

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**Table 1**
(*continued*)

| Organ/System | Thalassemia | SCD |
|---|---|---|
| cGVHD | • Evaluate every month while receiving immunosuppression<br>• Evaluate every 3 months for 2 years after stopping immunosuppression and as clinically indicated thereafter | • Evaluate every month when on immunosuppression<br>• Evaluate every 3 months off immunosuppression until 2 years and as clinically indicated thereafter |
| Quality of life | • Evaluate QOL in age-appropriate fashion at 1 year and as needed—education, social life, activity (children), employment, earning capacity, independence (adults)<br>• Track patient-reported outcomes (www.healthmeasures.net) | • Evaluate pain symptoms and medication use at each clinic visit<br>• Evaluate QOL in age-appropriate fashion at 1 year and as needed—education, social life, activity (children), employment, earning capacity, independence (adults)<br>• Track patient-reported outcomes (www.healthmeasures.net) |
| Healthcare utilization | • Consider tracking hospital admissions before, during, and after recovery from HCT | • Track hospital admissions before, during, and after recovery from HCT |
| Nutrition and metabolic function | • Evaluate yearly—fasting lipid profile, fasting glucose, blood pressure, BMI, waist circumference | • Evaluate fasting lipid profile, fasting glucose, blood pressure, BMI, waist circumference yearly |
| Screening for malignancy | • As indicated in age-appropriate fashion (skin, thyroid, breast, colon, prostate, cervix, testes) | • As indicated in age-appropriate fashion (skin, thyroid, breast, colon, prostate, cervix, testes) |

We recommend yearly post-HCT follow-up for the first 5 years. Subsequent transplant-related follow-up is recommended once every 2-3 years for the patient's lifetime. ASBMT indicates American Society for Blood and Marrow Transplantation; EBMT, European Society for Blood and Marrow Transplantation; cGVHD, chronic GVHD; PCN, penicillin; MRI, magnetic resonance imaging; GGT, γ-glutamyl transferase; PT, ; PFT, pulmonary function tests; TLC, total lung capacity; $FEV_1$, forced expiratory volume in 1 second; FVC, forced vital capacity; $DL_{CO}$, diffusing capacity of carbon monoxide; PRES, posterior reversible leukoencephalopathy syndrome; MRA, ; BUN, blood urea nitrogen; GFR, glomerular filtration rate; TSH, thyroid-stimulating hormone; FSH, follicl- stimulating hormone; LH, luteinizing hormone; GTT, glucose tolerance test; IGF, insulin-like growth factor; BMI, body mass index; vitamin D (25-OH), vitamin D (25 hydroxycholecalciferol).

* Serum ferritin is an acute phase reactant. It will be elevated in inflammatory conditions such as GVHD and is not a reliable indicator of iron over load in that setting.

pregnancy [21]. Transplanted patients should be advised that despite having a normal hemoglobin level after HCT, the thalassemia genes in the germline are transmissible.

## SCD TRANSPLANT-SPECIFIC FOLLOW-UP

The decision to pursue HCT for SCD is based on an assumption that physical symptoms and/or ongoing organ damage, including pulmonary or neurologic complications, can be stabilized or even improved with no further deterioration of organ function or SCD symptoms in the long-term. If organ damage is reversible and symptoms are resolved after HCT, these improvements should translate into a better health-related quality of life (HRQOL) [22,23]. Splenic function in SCD, for example, may recover in most young transplant recipients (<15 years old) and even in some older individuals, especially in the absence of chronic GVHD [24]. Early pulmonary or neurologic complications may be reversible to a variable extent [25]. Post-HCT follow-up is directed at establishing and tracking the positive and negative effects of HCT on sickle vasculopathy as expressed in target organs. It is very likely that the inflammatory milieu and pre-existing organ injury, which are common features of treating patients with severe SCD by HCT, predispose to transplant-related complications. These include sickle nephropathy and the development of hypertension during calcineurin inhibitor administration, hypogonadism, and the increased risk of GVHD in older SCD recipients.

Target organs and SCD-related complications that should be monitored before and after HCT include the CNS (ischemic or hemorrhagic infarcts, vasculopathy, atrophy, susceptibility to posterior reversible encephalopathy syndrome, decline in cognitive function), cardiopulmonary complex (pulmonary insufficiency, particularly restrictive pulmonary disease, pulmonary hypertension), chronic pain, renal complications (impaired glomerular filtration and urinary concentrating ability, renal insufficiency, hypertension), sickle retinopathy, priapism, gonadal dysfunction, RBC allo-immunization and post-HCT transfusion management, iron-related complications, and splenic function. Long-term follow-up guidelines recommended for identification and monitoring of SCD-specific complications and interventions are shown in Table 1.

## NEUROCOGNITIVE FOLLOW-UP

CNS impairments in SCD can be subtle or overt, and neurocognitive assessments can define important functional CNS domains. Because the plasticity of pre-existing CNS damage is uncertain, these tests also measure the effect of HCT itself on cognitive function. An informal survey at the Pediatric Blood and Marrow Transplant Consortium meeting revealed that reliable access to systematic neuropsychological evaluations was limited and often exacerbated by insurance and other psychosocial barriers. Thus, we offer the following operator- and nonoperator-dependent options for neuropsychological assessment after HCT. If a skilled neuropsychologist is available to participate in standard clinical care, we recommend they refer to the PhenX SCD website (https://www.phenxtoolkit.org/index.php?pageLink=about.scd). Some but not all PhenX protocols are also available in Spanish and Chinese languages. PhenX measures are periodically updated to facilitate appropriate neurocognitive studies in specific subgroups. This toolkit, developed by hemoglobinopathy experts, followed a consensus process with input from the scientific community. Selecting PhenX tests that are clearly defined, well established, low burden, reproducible, and easily available guided the development of these guidelines. Measures that had relevance across populations, were previously used in reference studies, and were accepted by the research community made ideal post-HCT comparators. Based on our knowledge of prevalent cognitive deficits in children with SCD, we recommend measurements of the domains listed in Table 2.

If neurocognitive function evaluation is not practical because of inadequate resources, a low-cost, low-burden alternative is available through the National Institutes of Health (NIH) Toolbox (http://www.healthmeasures.net/resource-center/nih-toolbox-ipad-app) for cognitive measures. Proof

**Table 2**
Recommended Measures of Cognition for Children with SCD

| Domain | Age Range | Measure |
|---|---|---|
| Intelligence | 6-16 years 11 months | Wechsler Intelligence Scale for Children, Fifth Edition |
| | 16-90 years | Wechsler Adult Intelligence Scale, Fourth Edition |
| | If age range spans 6 years through adulthood | Wechsler Abbreviated Scale of Intelligence, Second Edition |
| Sustained and selective attention | 8 years old and older | Conners Continuous Performance Test, 3rd Edition |
| Working memory | 5-16 years | Children's Memory Scale |
| Executive function | 5-18 years<br>Parent reported | Behavior Rating Inventory of Executive Function |
| | 18 years and older | Trail Making Test A and B |
| Adaptive behavior | Any age<br>Parent reported for child | Vineland Adaptive Behavior Scales, Second Edition |

**Table 3**
Tests of Cognition using the NIH Toolbox

| Type of Ability | Validated Assessment | Cognitive Function Addressed |
|---|---|---|
| Crystallized measures | Picture Vocabulary Test [27,28] | Intellectual achievement, demonstrated largely through vocabulary and general knowledge |
| | Oral Reading Recognition Test [27,28] | |
| Fluid measures | Picture Sequence Memory Test [29,30] | Episodic memory |
| | Pattern Comparison Processing Speed Test [31,32] | Processing speed |
| | List Sorting Working Memory Test [31,32] | Working memory |
| | Flanker Inhibitory Control and Attention Test [33,34] | Executive function/inhibitory control |
| | Dimensional Change Card Sort Test [33,34] | Executive function/cognitive flexibility |

of qualification to access cognitive assessment is required. In a clinical trial, a physician, psychologist, or healthcare provider with experience and/or training in this assessment can obtain access for a small fee. The investigator can access tests as an tablet application and oversee training with the application. Videos for training are available online (http://www.healthmeasures.net/NIH_Toolbox_iPad_e-learning/story_html5.html). In-person training is available from the HealthMeasures group. We recommend that clinical trial participants complete assessments from the NIH Toolbox Cognition Domain [26] using the NIH Toolbox tablet application as shown in Table 3. Executive function, attention, working memory, and processing speed can be assessed. In addition, the battery includes 2 tests of crystalized abilities (oral reading and vocabulary) as an estimate of pretransplant functioning for comparison purposes. It takes approximately 35 minutes to complete the cognitive tests. Additional research instruments that are relatively low burden but informative include true measures of intelligence such as an abbreviated Wechsler Abbreviated Scale of Intelligence, Second Edition, which takes approximately 15 minutes to administer and can be a serial reference point for intelligence. In a small SCD cohort, intelligence quotients improved at 3 and 5 years post-HCT [35]. We caution that meaningful evaluation depends on the maintenance of inter- and intrapatient consistency in testing. Additional effort may be necessary to accomplish testing because compliance may be challenging.

## HCT-RELATED COMPLICATIONS

HCT-related complications that require long-term follow-up after HCT for hemoglobinopathies include monitoring and management of mixed donor–host hematopoietic chimerism, complications of chronic GVHD and treatment, immune reconstitution and susceptibility to infections, and awareness/screening for malignant transformation after exposure to transplant conditioning regimens and immunosuppression [3]. Mixed chimerism is common after HCT for hemoglobinopathy, presumably because of recipient immune competence [36,37]. Although early mixed chimerism (within 2 years of HCT) can be a dynamic phenomenon with a risk of graft rejection and disease recurrence, late mixed chimerism > 2 years post-HCT (involving 10% to 15% of patients) is a more stable phenomenon, and graft rejection is rare [38]. Stable mixed chimerism usually generates the donor hemoglobin phenotype and is not distinguishable from full donor chimerism, with regard to clinical benefit [39].

The percentage of myeloid donor engraftment necessary to maintain a functioning graft in hemoglobinopathy patients is not known, but 1 recent publication reported ≥ 20% donor chimerism was necessary for a curative effect [37,40,41]. In contrast, a donor chimerism level of 12% has been reported to control SCD symptoms and was curative [42]. In HCT for SCD from a donor with trait, if the hemoglobin S level increases > 50%, disease recurrence follows. GVHD manifestations are similar to those in patients with malignant disorders, and incidence and severity vary according to the graft source, HLA compatibility, and patient age [43]. Depending on its severity, chronic GVHD can negatively affect long-term quality of life and requires monitoring and intervention for control [44,45]. The incidence of malignant disorders after HCT for thalassemia is <10 per 100,000 per year and does not appear to be higher than in patients with β-thalassemia major that are not transplanted [46,47]. The incidence of malignancy after HCT for SCD is unclear and should be monitored long term.

## GONADAL FUNCTION AND FERTILITY PRESERVATION

Two forms of gonadal insufficiency can occur after HCT in childhood: hypogonadotropic hypogonadism due to pituitary iron overload and hypergonadotropic hypogonadism due to gonadal damage from conditioning chemotherapy. Hormonal function in prepubertal boys is usually better preserved than fertility because Leydig cells are less sensitive to conditioning agents compared with spermatogonial cells [48,49]. Hormonal function and fertility are equally impaired in prepubertal girls, and ovarian insufficiency is very common after HCT postpuberty, particularly after exposure to myeloablative busulfan [50]. Baseline gonadal function (Tanner staging,

gonadotropin and hormone levels) should be assessed in all patients who are 11 years of age and older pre-HCT. After transplant, annual assessments of pubertal development, sexual, and reproductive function is recommended based on accelerated impairment after exposure to conditioning regimens (Supplemental Table S1). This includes luteinizing hormone, follicle-stimulating hormone, anti-Mullerian hormone, and estradiol levels in females and follicle-stimulating hormone, luteinizing hormone, and early morning testosterone levels in males who are 11 years of age and older. Evidence of abnormal pubertal timing or gonadal dysfunction should prompt early referral to an appropriate service such as endocrinology, gynecology, urology, and/or reproductive medicine.

Depending on the transplant method used and the age of the recipient, individualized discussion about the risks of gonadal dysfunction/infertility and options for fertility preservation are recommended pre-HCT. Postpubertal males can pursue sperm cryopreservation. Patients considering offspring post-HCT should be informed about genetic transmission of hemoglobinopathy to their children. Testicular tissue cryopreservation for ex vivo spermatogenesis and in vitro fertilization is experimental [51-53]. Similarly, postpubertal females can pursue options that include ovarian protection techniques by hormonal suppression with gonadotropin-releasing hormone agonists, embryo preservation, and oocyte or ovarian tissue cryopreservation [54-58]. Some of these methods are only available on research protocols and often must be paid out of pocket.

## ASSESSMENT OF HRQOL

HRQOL assessments after HCT are important tools for assessing the benefit of HCT in disorders that are not imminently life-threatening and can guide clinical decision-making. HRQOL assessments quantify broad nonorgan-specific impacts of a disease-free state and are influenced by transplant complications such as chronic GVHD. Although nuanced measurement batteries that dive deeply into the experiences of SCD and chronic GVHD are very informative if completed, less-specific tools can be easier to achieve repeatedly and matched across treatment options with ease. Assessments pre-HCT, at 6 months, 12 months, 2 years, and yearly beyond if indicated can provide global functional outcomes. Uniformity across clinical trials provides comparisons.

HRQOL assessment options used previously include the Child Health Questionnaire or the Pediatric Quality of Life Inventory 4.0 [22,59]. A newer option is the Patient-Reported Outcomes Measurement Information System, a set of person-centered measures that evaluates and monitors physical, mental, and social health. Self and parent proxy measures are available, and several of the domains like fatigue, pain intensity, and peer relationships are particularly relevant to children with SCD. The Patient-Reported Outcomes Measurement Information System has been validated in multiple populations with chronic conditions and is free to use (http://www.healthmeasures.net/explore-measurement-systems/promis) [60-65].

A complete pediatric evaluation of HRQOL includes both child and parent reports in an age-dependent fashion. The routine use of post-transplant HRQOL assessments irrespective of clinical trials, although challenging in busy clinical practice settings, can be an important and useful long-term outcome measure for providers, patients, and families.

## ASSESSMENT OF HEALTHCARE UTILIZATION

The cost of healthcare in hemoglobinopathy patients increases with age and frequency of complications [66]. Transplant costs, however, are highest when in the first year after the transplant is performed [67]. Hospital admissions and health maintenance costs subsequently decrease in most cases, unless there are significant transplant-related complications with prolonged hospitalizations. Tracking all costs related to healthcare utilization post-HCT provides a comparison with the costs associated with supportive care in hemoglobin disorders and has economic significance for payors and patients.

## CONCLUSION

In summary, this report presents concise guidelines that can be incorporated into clinical trial design and routine clinical post-transplant follow-up care to track the impact of HCT on patients with hemoglobin disorders. Standardizing outcome measurements and ensuring global follow-up across various treatment options such as supportive care, transplant, and therapy with gene-modified cells can provide objective information regarding the therapeutic intervention, inform differences between treatment modalities, and help with decision-making for patients, providers, and families.

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## SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at doi:10.1016/j.bbmt.2018.04.002.

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