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Late Effects Screening Guidelines after Hematopoietic Cell Transplantation (HCT) for Inherited Bone Marrow Failure Syndromes (IBMFS): Consensus Statement from the Second Pediatric Blood and Marrow Transplant Consortium International Conference on Late Effects after Pediatric HCT

Andrew C. Dietz[1], **Sharon A. Savage**[2], **Adrianna Vlachos**[3], **Parinda A. Mehta**[4], **Dorine Bresters**[5], **Jakub Tolar**[6], **Carmem Bonfim**[7], **Jean Hugues Dalle**[8], **Josu de la Fuente**[9], **Roderick Skinner**[10], **Farid Boulad**[11], **Christine N. Duncan**[12], **K. Scott Baker**[13], **Michael A. Pulsipher**[1], **Jeffrey M. Lipton**[3], **John E. Wagner**[6,*], and **Blanche P. Alter**[2,*]

[1]Children's Center for Cancer and Blood Diseases, Children's Hospital Los Angeles, University of Southern California, Los Angeles, California, USA [2]Clinical Genetics Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, Maryland, USA [3]Hofstra Northwell School of Medicine, Feinstein Institute for Medical Research, Cohen Children's Medical Center, Division of Hematology/Oncology and Stem Cell Transplantation, New Hyde Park, New York, USA [4]Division of Bone Marrow Transplantation and Immune Deficiency, Cancer and Blood Diseases Institute, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio; Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, Ohio, USA [5]Willem-Alexander Children's Hospital, SCT Unit, Leiden University Medical Center, Leiden, The Netherlands [6]Blood and Marrow Transplant Program, University of Minnesota, Minneapolis, Minnesota, USA [7]Hospital de Clinicas, Federal University of Parana, Curitiba, Brazil [8]Université Paris 7, Hôpital Robert-Debré, Service d'hématoimmunologie, Paris, France [9]Section of Paediatrics, Imperial College, London, UK Department of Paediatric Haematology, St Mary's Hospital, Imperial College Healthcare NHS Trust, London, United Kingdom [10]Great North Children's Hospital, Newcastle upon Tyne Hospitals NHS Foundation Trust and Northern Institute of Cancer Research, Newcastle University, Newcastle upon Tyne, United Kingdom [11]Bone Marrow Transplant Service, Department of Pediatrics, Memorial Sloan Kettering Cancer Center, Division of Pediatric Hematology/Oncology, New York Presbyterian Hospital, Weill Cornell Medical College, New York, New York, USA [12]Dana-Farber/Boston Children's Cancer and Blood Disorders Center, Boston,

Corresponding Author: Andrew C. Dietz, MD, MSCR, Assistant Professor of Clinical Pediatrics, USC Keck School of Medicine, Blood and Marrow Transplantation Section, Division of Hematology, Oncology and Blood & Marrow Transplantation, Children's Hospital Los Angeles, 4650 Sunset Blvd., Mailstop #54|, Los Angeles, CA 90027, Ph: 323.361.2546, Fax: 323.361.8068, adietz@chla.usc.edu.

*Both authors contributed equally

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Massachusetts, USA [13]Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, Washington, USA

Abstract

Patients with inherited bone marrow failure syndromes (IBMFS) such as Fanconi anemia (FA), dyskeratosis congenita (DC), and Diamond Blackfan anemia (DBA) can have hematologic manifestations cured through hematopoietic cell transplantation (HCT). Subsequent late effects seen in these patients arise from a combination of the underlying disease, the pre-HCT therapy, and the HCT process. During the international consensus conference sponsored by the Pediatric Blood and Marrow Transplant Consortium entitled "Late Effects Screening and Recommendations Following Allogeneic Hematopoietic Cell Transplant for Immune Deficiency and Nonmalignant Hematologic Disease" held in Minneapolis, Minnesota in May of 2016, a half-day session was focused specifically on the unmet needs for these patients with IBMFS. This multidisciplinary group of experts in rare diseases and transplantation late effects has already published on the state of the science in this area along with discussion of an agenda for future research. This companion article outlines consensus disease specific long-term follow-up screening guidelines for patients with IMBFS.

Keywords

late effects; pediatric allogeneic hematopoietic cell transplant; inherited bone marrow failure syndromes; Fanconi anemia; dyskeratosis congenita; Diamond Blackfan anemia

Background

Increasing indications for allogeneic hematopoietic cell transplantation (HCT) in childhood diseases[1–3] and improved survival post-HCT lead to projection that there will be more than 70,000 childhood HCT survivors under the age of 18 years at transplantation by 2030 in the United States alone.[1] Children undergoing HCT for nonmalignant diseases, including inherited bone marrow failure syndromes (IBMFS), immune system disorders, and hemoglobinopathies represent a growing number of patients with special follow-up needs.[4]

Much of our understanding of long-term toxicities in survivors of pediatric HCT comes from the study of patients with hematological malignancies. There is a high burden of late effects and mortality compared with the general population[5] as well as in comparison to childhood cancer survivors treated with chemotherapy and/or radiation. Known risk factors include younger age at HCT, the use of total body irradiation (TBI) and chronic graft versus host disease (GVHD).[6–14] Recent reports have examined populations with much larger proportions of nonmalignant HCT survivors.[15] There are now single center and smaller consortia reports showing that long-term complications are common in survivors of transplantation for IBMFS, hemoglobinopathies and immune deficiencies.[16–27]

General HCT follow-up guidelines have been created,[28–31] reviewed,[32] and are summarized in Table 1. These guidelines do not consider pre-transplant exposures or disease-specific

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manifestations that are unique to patients with nonmalignant hematopoietic disorders, and cannot be readily interchanged with exposures for malignant disease such as chemotherapy and radiation. Furthermore, the interaction of each specific nonmalignant disorder with the HCT process may alter the natural history and risk of late effects. This is important for understanding how to screen, diagnose and treat or prevent these complications. These issues were discussed at the Second International Pediatric Blood and Marrow Transplant Consortium (PBMTC) Consensus Conference on Late Effects after Pediatric Hematopoietic Cell Transplantation in Minneapolis in May, 2016. The current state of knowledge as well as an agenda for future research specific to IBMFS has previously been published by this group,[33] and is summarized here in support of the surveillance recommendations.

Table 1 presents a starting point for these new long-term follow-up recommendations tailored to each individual IBMFS. Consensus recommendations provided are meant to outline an ideal follow-up from which to move forward. It should also be noted that there are limited data on the long-term follow-up post-HCT for these disorders, making it difficult to create evidence-based guidelines for the management of IBMFS and thus this work is based upon a combination of available data and expert opinion. Additionally, gene therapy is not addressed in these recommendations. However, as it is employed as a therapeutic modality for these children, it may require different approaches to follow up. An important area of consideration for all genetic diseases includes the need for genetic counseling, family planning, and counseling regarding living with chronic conditions. Of note, within the broad diagnostic categories of FA, DC and DBA, there are a myriad of causative pathogenic germline variants in multiple genes, many conferring very specific phenotypes. This variability may have a bearing on transplant related morbidity and mortality as well as late effects in survivors. Although it is beyond the scope of these guidelines a detailed assessment of each patient, with this in mind, is essential. This has been outlined in detail for FA (http://fanconi.org/index.php/publications/guidelines_for_diagnosis_and_management) and DC (https://www.dcoutreach.org/guidelines) in previously published clinical guidelines.

Fanconi Anemia (FA)

Five-year survival after a matched sibling transplant for FA is now approximately 90%, with similar improvements after alternative donor transplant.[24, 34–37] Many patients with FA are now surviving to adulthood post-HCT and long-term side effects of HCT are becoming more apparent. FA is the most studied of the IBMFS to date with respect to late effects after HCT. The follow-up of patients with FA who have had an HCT may differ from follow-up of patients post-HCT for other indications and from the management of non-transplanted patients with FA, with regard to non-hematologic systems, such as endocrine manifestations and cancer risk. Table 2 summarizes the recommended FA specific late effects screening guidelines.

The wide variety of FA-related complications, including those related to congenital anomalies, indicates that detailed attention needs to be paid to these problems before, during, and long after HCT. This can include neurodevelopmental issues as well as genitourinary, renal, cardiac, gastrointestinal, and musculoskeletal anomalies.[38, 39] Patients with FA who progressed to severe marrow failure may have been previously treated with

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transfusion support. Multiple red blood cell transfusions without adequate iron chelation may lead to iron overload in the liver, heart and endocrine organs. Timely and aggressive screening and management for iron overload are recommended.

Endocrinopathies including thyroid dysfunction, growth hormone deficiency, glucose intolerance, and gonadal dysfunction are common in patients with FA independent of HCT, and in fact these can be exacerbated in post-HCT period.[40–43] Routine and comprehensive follow-up with an endocrinology team is strongly recommended and remains a key area of post-HCT follow-up care.

The risk of acute myeloid leukemia (AML) and myelodysplasia (MDS) is markedly decreased by the HCT, while solid tumors, most notably squamous cell carcinoma (SCC) of head and neck and genital region, remain the most common malignancies.[44] *Oral cavity* SCC in patients with FA is not associated with human papillomavirus (HPV) in the same way as *oropharyngeal* SCC is in the general population.[45] However, HPV vaccination is still recommended for prevention of HPV-associated genital SCC regardless of gender. While chronic GVHD involving the mouth and/or genitourinary tract has a strong association with the risk of SCC, the impact of radiation is less clear but remains a possible risk factor.[23, 24, 46–50] Whether busulfan or lowering the total dose and dose rates of radiation or shielding has altered the risk of cancer remains to be determined. Importantly, patients whose FA is due to mutations in *FANCD1/BRCA2* or *FANCN/PALB2* need genotype-specific cancer screening because of increased risks of medulloblastoma, Wilms tumor and other cancers.[51–54]

The long-term follow-up issue that deserves the greatest degree of attention in patients with FA post-HCT is the apparent increased risk of cancer.[55] Importance of screening for these cancers is increasingly recognized by the development of specifically designed surveillance schedules.

Dyskeratosis Congenita (DC)

Survival for patients with DC after transplant has not reached the levels of FA, but there have been significant improvements over time[56] such that more patients with DC are living much longer after HCT. In contrast to FA, DC-associated bone marrow failure develops more gradually, with a cumulative incidence of 40% by about age 40,[48] and thus DC patients may be older than those with FA when they undergo HCT. Although long-term events, whether disease related and/or late effects after HCT, are becoming more apparent, there are limited data on long-term follow-up after HCT in this population. Important differences in HCT follow-up practices exist compared to otherwise standard HCT follow-up with respect to non-hematological manifestations of DC and cancer risk. Table 3 summarizes the recommended DC specific late effects screening guidelines.

There are a wide variety of DC-related complications, including progression of the clinical manifestations, and thus detailed attention needs to be paid to these problems before, during, and long after HCT. These include neurodevelopmental issues as well as genitourinary anomalies and visual problems.[39, 57, 58] Life-threatening issues include pulmonary fibrosis,

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liver cirrhosis, enteropathy, gastrointestinal bleeding, and pulmonary arterio-venous malformations.[39, 57, 58] Patients with DC who progressed to severe marrow failure may have been treated in the past with transfusion support, and multiple transfusions may lead to iron overload in the liver, heart, and endocrine organs. Thus, early and aggressive screening and management should occur for iron overload. Comprehensive review of case reports and case series indicate that the major late adverse events are pulmonary disease, liver disease, and vascular complications. These complications differ from infection, graft failure and hemorrhage, that are the most common early causes of mortality following HCT in other contexts.[56] Surveillance and timely intervention for these late deadly complications are important, since there are reports of successful lung or liver transplantation in DC patients.[59, 60] Osteoporosis and osteopenia are commonly reported in DC[57] and can get worse post-HCT from the use of steroids. Surveillance for and optimizing good bone health post-HCT may also help with avascular necrosis of the hips and shoulders which at times require hip replacement surgery at young age.

The risk of AML and MDS is markedly decreased by HCT, and thus solid tumors, most notably SCC of head and neck and genital region, remain the most common malignancies.[48, 57, 61] There are very little data about the association between HPV and *oral cavity* SCC in DC though notably, one study of head and neck SCC in four DC patients did not detect HPV in the tumors.[45] However, HPV vaccination is recommended for prevention of HPV-associated genital SCC regardless of gender. Similarly, a close follow-up with dermatology is an integral part of post-HCT care due to the increased risk of skin SCC.

The long-term follow-up issues that may occur with aging, but that deserve the greatest degree of attention in patients with DC post-HCT are pulmonary fibrosis, liver fibrosis, pulmonary arteriovenous malformation, gastrointestinal bleeding, and increased risk of SCC.

Diamond Blackfan Anemia (DBA)

Increasing numbers of patients are receiving HCT for the anemia of DBA with improved survival,[62–64] and thus long-term events, whether disease related and/or late effects after HCT, are also becoming more apparent. There are few data on long-term follow-up after HCT in this population. Important differences in HCT follow-up practices exist compared to otherwise standard HCT follow-up with respect to non-hematological manifestations of DBA and cancer risk. Table 4 summarizes the recommended DBA specific late effects screening guidelines.

The variety of DBA-related complications, including craniofacial, cardiac, genitourinary, renal, and musculoskeletal anomalies[65, 66] require multiple subspecialty care teams throughout the entire pre-and post-HCT period. The other major issues patients with DBA face through the transplant process and into longer-term follow-up are related to prior history of regular transfusions and long-term corticosteroid use. Significant endocrinopathies including problems with bone health are of particular concern.[66, 67] The impact of iron burden specifically presents one of the major challenges for DBA patients and the importance of optimization of the same prior to transplant cannot be underrated.[68] Iron

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abatement via chelation must be addressed pre-HCT with additional post-HCT phlebotomy or chelation to prevent cardiac or hepatic complications.

The risk of AML and MDS is markedly decreased by HCT, but solid tumors, most notably luminal gastrointestinal cancers and osteosarcoma, remain the most common malignancies in patients with DBA.[69, 70] Individualized cancer screening practices need to evolve with recognition of these risks and better understanding of the impact HCT adds to the risk of developing these and other cancers. Also, it should be noted that a reduced intensity HCT with partial chimerism may not fully mitigate the risk of AML and MDS.

The long-term follow-up issues that deserve the greatest degree of attention in patients with DBA post-HCT are iron overload, much of which is carried over from pre-HCT treatment, and the increasing solid tumor risk as patients with DBA age.

Conclusion

This document outlines late effects screening guideline recommendations for patients with IBMFS post-HCT that have been developed through an international collaboration and consensus process. These recommendations are meant to outline an ideal follow-up as a starting point for management of these patients moving forward. With consistency in follow-up and continued observation of these patients post-HCT, we hope to learn additional information that will lead to modification of these guidelines over time. These recommendations focus on FA, DC, and DBA, but it is important to understand and develop syndrome-specific guidelines for all patients who undergo HCT for nonmalignant disease.

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Table 1

General Late Effects Screening Guidelines after Hematopoietic Cell Transplantation

Late Effect/Organ System	Summary of General HCT Late Effects Guidelines

Immune Reconstitution/Immunologic	• Patients with GVHD on immune suppression:
	  ○ Encapsulated organism and pneumocystis antibiotic prophylaxis
	  ○ Broad spectrum parenteral antibiotics for fevers
	  ○ Regular screening for CMV and/or other opportunistic infections
	• Endocarditis prophylaxis according to AHA guidelines
	• Annual evaluations for recurrent, unusual, or severe infections
	• Screening for HIV and Hepatitis in those exposed to blood products
	• Immunizations according to published guidelines
	• Monitoring of T cell and B cell immune reconstitution
	• Monitoring of T cell proliferative capacity to mitogens
	• Neoantigen challenge for patients with poor immune reconstitution

Iron Overload	• Serum ferritin screening post-HCT, repeat annually or as needed until normal • Consider T2* MRI if screen positive or significant transfusion history • Follow LFTs regularly and consider hepatology consult if elevated • Phlebotomy or chelation therapy for management if iron burden clinically significant
Neurocognitive	• Yearly screening for educational and developmental progress • Neuropsychological evaluation at minimum one year post-HCT, repeat as needed • Referral to appropriate school or other resources for those with identified neurocognitive deficits
Subsequent Cancer Risk	• Lifestyle counseling to avoid high-risk behaviors and encourage good behaviors (e.g. smoking, excessive alcohol, sunscreen use, healthy diet, exercise, etc.) • Annual history and physical • Encourage self-exam (e.g. skin, oral cavity, genitalia) • Follow general population cancer screening guidelines • Regular dental exams for those with chronic GVHD • Mammography in women beginning at age 25 or 8 years after TBI or chest radiation exposure (no later than age 40), with consideration for breast MRI in some patients
Pulmonary	• Annual history and physical • Counsel regarding tobacco avoidance or cessation • PFT every 6 to 12 months initially, then as clinically indicated • Focused radiological exam for those with abnormal findings • Referral to pulmonologist with abnormal findings
Reproductive/Gonadal	• At least annual assessment of pubertal development, sexual and reproductive function • LH, FSH, and testosterone in males, consider semen analysis • LH, FSH, and estradiol in females, with some centers using AMH screening • Referral to endocrinologist, gynecologist, or urologist with abnormal pubertal timing or gonadal dysfunction • Treat ovarian failure with hormone replacement therapy

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Late Effect/Organ System	Summary of General HCT Late Effects Guidelines
	• Counsel about birth control in those of reproductive age
Renal	• At least annual hypertension screening • At least annual urinalysis, urine protein or albumin to creatinine ratio, serum creatinine, and BUN • Referral to nephrologist if hypertension or renal dysfunction
Growth	• At least annual height, weight, BMI, and Tanner staging • Annual thyroid function, bone age, and refer to endocrinologist for abnormal growth rate or other abnormalities
Psychosocial	• At least annual assessment for mental health concerns, chronic pain and fatigue, risky behaviors, and access to health care • Encouragement of robust support networks • Additional assessment of family members and caregivers • Referral to mental health professional as needed

HCT, hematopoietic cell transplantation; GVHD, graft-versus-host disease; CMV, cytomegalovirus; AHA, American Heart Association; HIV, human immunodeficiency virus; MRI, magnetic resonance imaging; LFTs, liver function tests; TBI, total body irradiation; PFT, pulmonary function testing; LH, lutein hormone; FSH, follicle-stimulating hormone; AMH, anti-mullerian hormone; BUN, blood urea nitrogen; BMI, body mass index

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Table 2

Late Effects Screening Guidelines after Hematopoietic Cell Transplantation for Fanconi Anemia

Late Effect/Organ System	Fanconi Anemia Specific Guidelines
Immune Reconstitution/Immunologic	• Ensure HPV vaccination
Iron Overload	• Earlier and more aggressive evaluation and management starting at 6 months post-HCT
Neurocognitive	• Attention to FA-associated neurodevelopmental issues
Subsequent Cancer Risk	• Dermatology: skin cancer screening every 6–12 months • Monthly oral self exam, dental exam every 6 months, and ENT evaluation every 6–12 months by head and neck physician, including nasolaryngoscopy (more frequent if unable to do self exam) • Increased screening for SCC in those with chronic GVHD and in those with *BRCA2* gene mutations, specifically to look for medulloblastoma and Wilms tumor
Pulmonary	• Follow-up as needed
Reproductive/Gonadal	• Follow-up of congenital genitourinary anomalies with a urologist • Yearly gynecologic evaluation for females with Pap smear and HPV screening, starting in the early teenage years • Measure serum AMH as a potential early marker of gonadal insufficiency, with consideration for fertility preservation measures
Renal	• Follow-up congenital renal anomalies and renal function with a nephrologist
Growth	• Full endocrine evaluation including GH levels (potentially with stimulation testing), IGF1, IGFBP3, Tanner staging and bone age • Monitor weight and assess for FA-associated failure to thrive
Psychosocial	• Inclusion of genetic counseling for patient and family • Assistance with family planning • Counseling about living with chronic conditions
Cardiac	• Follow up with cardiology for congenital cardiac anomalies and screen with ECG and Echocardiogram
Endocrine	• Screening for diabetes, dyslipidemia, and Vitamin D deficiency • Screening for osteoporosis with DEXA pre-HCT and every 2 years post-HCT • Screening for avascular necrosis if bone or joint pain develop
Other	• Screening for vision and cataracts • Screening for hearing loss if clinically indicated • Follow LFT regularly and consider hepatology consult if elevated • Follow-up of congenital musculoskeletal anomalies and evaluation for scoliosis • Lifestyle counseling to promote good health habits: encourage healthy diet and regular exercise, avoid alcohol, smoking, and second-hand smoke, limit sun exposure and use sunscreen

HPV, human papilloma virus; HCT, hematopoietic cell transplantation; ENT, ears, nose, and throat physician; SCC, squamous cell carcinoma; GVHD, graft-versus-host disease; AMH, anti-mullerian hormone; GH, growth hormone; IGF1, insulin-like growth factor 1; IGFBP3, insulin-like growth factor binding protein 3; ECG, electrocardiogram; DEXA, dual-energy x-ray absorptiometry; LFT, liver function tests

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Table 3

Late Effects Screening Guidelines after Hematopoietic Cell Transplantation for Dyskeratosis Congenita

Late Effect/Organ System	Dyskeratosis Congenita Specific Guidelines
Immune Reconstitution/Immunologic	• Ensure HPV vaccination
Iron Overload	• Earlier and more aggressive evaluation and management starting at 6 months post-HCT
Neurocognitive	• Attention to DC-associated neurodevelopmental issues, particularly in those with HH or Revesz syndromes
Subsequent Cancer Risk	• Dermatology for skin cancer screening every 6–12 months • Monthly self oral exam, dental exam every 6 months, and ENT evaluation yearly by head and neck physician, including nasolaryngoscopy (more frequent if unable to do self exam)
Pulmonary	• Lifelong pulmonary symptom screening for DC-associated pulmonary fibrosis and other post-HCT issues • PFT screening yearly with low threshold for referral to pulmonologist for decline in lung function • Surveillance for pulmonary AVM with low threshold for bubble echo prior to HCT as well as in long-term follow-up depending on pre-HCT results and symptoms
Gastrointestinal	• Screening for esophageal stenosis with treatment as needed • Surveillance for bleeding, ulceration, telangiectasias, and varices as clinically indicated • Follow LFTs regularly and consider hepatology consult if elevated for DC-associated liver cirrhosis and fibrosis
Reproductive/Gonadal	• Follow-up of congenital genitourinary anomalies with a urologist • Examination for urethral stenosis, which may need dilation • Yearly gynecologic evaluation for females with Pap smear and HPV screening
Renal	• Follow-up as needed for congenital genitourinary anomalies and related renal dysfunction if present
Growth	• Full endocrine evaluation including GH levels (potentially with stimulation testing), IGF1, IGFBP3, Tanner staging, and bone age • Measure weight and assess for DC-associated failure to thrive
Psychosocial	• Inclusion of genetic counseling for patient and family • Assistance with family planning • Counseling about living with chronic conditions
Other	• Screening for vision, lacrimal duct stenosis, retinal pathology, and cataracts • Screening for hearing loss • Lifestyle counseling to promote good health habits: encourage healthy diet and regular exercise, avoid alcohol, smoking, and second-hand smoke, limit sun exposure and use sunscreen • Screening for osteoporosis with DEXA pre-HCT and every 2 years post-HCT • Evaluate for avascular necrosis if bone or joint pain develop

HPV, human papilloma virus; HCT, hematopoietic cell transplantation; HH, Hoyeraal-Hreidarsson; ENT, ears, nose, and throat physician; GVHD, graft-versus-host disease; PFT, pulmonary function testing; AVM, arteriovenous malformation; LFTs, liver function tests; GH, growth hormone; IGF1, insulin-like growth factor 1; IGFBP3, insulin-like growth factor binding protein 3; DEXA, dual-energy x-ray absorptiometry

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Table 4

Late Effects Screening Guidelines after Hematopoietic Cell Transplantation for Diamond Blackfan Anemia

Late Effect/Organ System	Diamond Blackfan Anemia Specific Guidelines
Immune Reconstitution/Immunologic	• Ensure HPV vaccination
Iron Overload	• Likely to be one of the major issues both pre- and post-HCT, with need for the earliest and most aggressive evaluation and management pre- and post-HCT • T2* MRI (for both hepatic and cardiac iron load) in addition to ferritin yearly until iron overload is resolved • Follow LFTs regularly and consider hepatology consult if elevated • Phlebotomy or chelation therapy as appropriate for management
Endocrine	• Complete endocrine evaluation is necessary as any/all endocrine organs can have organ dysfunction (thyroid, parathyroid, pancreatic, adrenal, gonadal, hypothalamic and pituitary) from iron overload
Neurocognitive	• Attention to neurodevelopmental issues, particularly in those patients with craniofacial abnormalities and large ribosomal protein gene deletions
Subsequent Cancer Risk	• Surveillance strategies for luminal GI cancers, osteosarcoma, and others are being developed for these patients and will apply post-HCT as well
Pulmonary	• Follow-up as needed
Reproductive/Go nadal	• Follow-up of congenital genitourinary anomalies with a urologist and full endocrine evaluation mentioned above
Renal	• Follow-up congenital renal anomalies with a nephrologist
Growth	• Full endocrine evaluation including GH levels (potentially with stimulation testing), IGF1, IGFBP3, Tanner staging, and bone age
Psychosocial	• Inclusion of genetic counseling for patient and family • Assistance with family planning • Counseling about living with chronic conditions
Other	• Screening for vision and cataracts (especially with pre-HCT steroid use) • Follow congenital cardiac anomalies and screen with ECG and Echocardiogram in addition to MRI T2* mentioned above • Follow-up of all congenital anomalies • Lifestyle counseling to promote good health habits: encourage healthy diet and regular exercise, avoid alcohol, smoking, and second-hand smoke, limit sun exposure and use sunscreen

HPV, human papilloma virus; HCT, hematopoietic cell transplantation; MRI, magnetic resonance imaging; LFTs, liver function tests; GI, gastrointestinal; GH, growth hormone; IGF1, insulin-like growth factor 1; IGFBP3, insulin-like growth factor binding protein 3; ECG, electrocardiogram