

RECOMMENDED POST-TRANSPLANT CARE

Part II: Screening for chronic GVHD



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Early detection of chronic graft-versus-host disease (GVHD) can help prevent irreversible organ damage, improve survival and increase the quality of life of your transplant recipient.

Chronic GVHD, an immune response of the donor-derived T cells against recipient tissues, occurs in approximately 30–70% of patients receiving an allogeneic transplant. This is a serious, potentially life-threatening post-transplant complication. However, with ongoing surveillance, judicious management and coordination of care, most cases of chronic GVHD resolve within five years and the median duration of treatment is 2–3 years.

Chronic GVHD is also associated with a lower rate of disease relapse due to a graft-versus-malignancy effect mediated by the donor-derived T cells. However, uncontrolled chronic GVHD is associated with increased non-relapse mortality, significant morbidity and impairments in health-related quality of life. Therefore, although low-grade chronic GVHD is associated with overall disease-free survival, it is still essential to treat active chronic GVHD.



Important care principles

- Early detection and definitive diagnosis are essential for successful treatment
- Definitive diagnosis of chronic GVHD requires excluding other diagnoses such as infection, drug effects, malignancies and residual post-inflammatory damage and scarring
- Involvement of multidisciplinary team is essential
- Both topical and/or systemic treatment may be appropriate
- Infection prophylaxis and prompt and effective management of infections are crucial; infection is a leading cause of death in chronic GVHD
- Long-term follow-up is required to monitor for late sequelae

Signs and symptoms of chronic GVHD

These guidelines are based on published diagnostic criteria from the National Institutes of Health (NIH) Consensus Development Project on chronic GVHD^{1,2,3} (see references on page 22). The following chart identifies clinical manifestations that are potential early indicators of chronic GVHD. If GVHD is suspected, it is recommended that you ***collaborate with the patient's transplant center to confirm the diagnosis and to develop and evaluate a treatment plan.*** Your early detection and contributions to effective management can help ensure the best survival and quality of life of your transplant recipient.

Organ/Sites	Evaluation	Clinical Manifestation	Description of Clinical Manifestation	Photo Atlas
Skin	Clinical examination <ul style="list-style-type: none"> • Complete visual examination of the skin with particular attention to pigmentary changes, rashes, textural changes, tightness, areas of thickening or skin breakdown, ulcers or erosions • Palpation for areas of sclerosis or fasciitis Diagnostic testing <ul style="list-style-type: none"> • Skin biopsy Patient-reported symptoms and signs <ul style="list-style-type: none"> • Itching • Dry skin • Limited mobility • Rash • Sores • Changes in skin coloring or texture • Edema 	Poikiloderma	Atrophic and pigmentary changes (with erythema and hypo and hyperpigmentation)	1
		Lichen planus-like features	Erythematous/violaceous flat-topped papules or plaques with or without surface reticulations or a silvery or shiny appearance on direct light	4, 5
		Sclerotic features	Smooth, waxy, thickened, tight, indurated skin and soft tissues caused by deep and diffuse sclerosis over a wide area	8, 9, 10
		Lichen sclerosus-like features	Discrete to coalescent gray to white moveable papules or plaques, often with follicular plugs, with a shiny appearance and leathery consistency	6
		Morphea-like features	Localized patchy areas of moveable smooth or shiny skin with leathery consistency, often with dyspigmentation	2
		Keratosis pilaris**	Pale to erythematous perifollicular papules with spiny keratotic plugs within the follicular openings	3
		Maculopapular rash***	Raised and flat small, red lesions	12

(Skin continued on next page.)

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** Rare, controversial, or non-specific features of chronic GVHD.

*** Common in both acute and chronic GVHD.

Organ/Sites	Evaluation	Clinical Manifestation	Description of Clinical Manifestation	Photo Atlas
Skin	Clinical examination <ul style="list-style-type: none"> • Complete visual examination of the skin with particular attention to pigmentary changes, rashes, textural changes, tightness, areas of thickening or skin breakdown, ulcers or erosions • Palpation for areas of sclerosis or fasciitis Diagnostic testing <ul style="list-style-type: none"> • Skin biopsy Patient-reported symptoms and signs <ul style="list-style-type: none"> • Itching • Dry skin • Limited mobility • Rash • Sores • Changes in skin coloring or texture • Edema 	Sweat impairment**	May manifest as heat intolerance due to loss of sweat glands	
		Ichthyosis**	Rough, thick and scaly skin	
		Hypopigmentation**	Diminished pigmentation of the skin	8
		Hyperpigmentation**	Darkening of the skin due to pigment deposition	4, 7, 8
		Depigmentation*	Loss of normal pigmentation	
		Erythema***	Abnormal redness of the skin	
		Pruritus***	Localized or generalized itching	
		Erosion ³	Localized skin lesion characterized by complete or partial loss of only the epidermis	11
		Ulcer ³	Localized skin lesion in which the whole of the epidermis and at least part of the dermis has been lost. May extend into the subcutaneous fat	

Organ/Sites	Evaluation	Clinical Manifestation	Description of Clinical Manifestation	Photo Atlas
Nails	Clinical examination <ul style="list-style-type: none"> • Visual inspection of nails Diagnostic testing N/A Patient-reported symptoms and signs <ul style="list-style-type: none"> • Brittle nails • Increased ridging in nails • Splitting nails • Nail loss 	Dystrophy*	Longitudinal ridging, splitting or brittle features	13
		Onycholysis*	Loosening of a nail from the nail bed beginning at the free edge and proceeding to the root	
		Nail loss*	Usually symmetric; affects most nails	
		Pterygium unguis*	Forward growth of the cuticle over the nail	
Scalp/ body hair	Clinical examination <ul style="list-style-type: none"> • Visual inspection of scalp hair/body hair for changes in hair distribution, consistency and color Diagnostic testing N/A Patient-reported symptoms and signs <ul style="list-style-type: none"> • Premature gray or thinning hair • Itchy scalp • Hair loss 	New onset of scarring or non-scarring scalp alopecia*	May also include loss of body hair (after initial recovery of hair growth following chemotherapy or radiotherapy)	14
		Scaling, papulosquamous lesions*	An eruption composed of papules and scales	
		Thinning scalp hair**		
		Premature gray hair**		

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³ See references on page 22.

Organ/Sites	Evaluation	Clinical Manifestation	Description of Clinical Manifestation	Photo Atlas
Eyes	Clinical examination <ul style="list-style-type: none"> • Visual inspection of the conjunctivae and sclerae • Ophthalmologic exam Diagnostic testing <ul style="list-style-type: none"> • Schirmer tear test • Slit-lamp examination Patient-reported symptoms and signs <ul style="list-style-type: none"> • Dry, burning, gritty eyes • Itching • Orbital pain • Difficulty opening eyes in the morning • Sensitivity to light and wind • Excessive tearing • Diminished visual acuity and/or blurring 	New onset dry, gritty or painful eyes*	New ocular sicca documented by low Schirmer test values with a mean value of both eyes ≤ 5 mm of wetting at 5 minutes	
		Cicatricial conjunctivitis*	Fibrous tissue scarring and inflammation	
		Keratoconjunctivitis sicca*	Inflammation of cornea and conjunctivae, with dryness, grittiness and/or orbital pain. Slit lamp exam may reveal punctate keratopathy and corneal or conjunctival surface staining. Schirmer tear test values < 5 mm of wetting	22, 23
		Confluent areas of punctate keratopathy*	Closely spaced, non-inflamed pinpoint defects indicating loss of corneal epithelium, and observed with fluorescein staining	
		Photophobia**	Increased sensitivity to light	
		Periorbital hyperpigmentation**	Excess pigmentation in the tissues surrounding or lining the orbit of the eye	
Blepharitis**	Erythema of the eyelids and/or eyelash follicles with edema	24		

Organ/Sites	Evaluation	Clinical Manifestation	Description of Clinical Manifestation	Photo Atlas
Mouth	Clinical examination • Visual inspection of the entire mouth Diagnostic testing • Oral biopsy Patient-reported symptoms and signs • Restriction of mouth opening • Dryness • Chapped lips • Ulcers • Swelling, redness, pain and/or bleeding of gums • Sensitivity to spicy foods, toothpaste or soda pop • Pain	Lichen planus-like changes	White lines and lacy-appearing lesions of the buccal mucosa, tongue, palate or lips	16
		Hyperkeratotic plaques	Thickened white patches of epithelium	19, 20
		Restriction of mouth opening	Restriction due to sclerosiis	
		Xerostomia*	Abnormal dryness of the mouth	
		Mucoceles*	Vesicle-like or raised masses due to minor salivary gland inflammation and damage	17
		Mucosal atrophy*	Thinning of mucosal tissue	19
		Pseudomembranes*	Loosely adherent fibrinous exudate on the surface of a mucous membrane	20
		Ulcers*	Open sore inside mouth caused by a break in mucous membrane or epithelium on lips or surrounding mouth	20, 21
		Erythema***	Severity of erythema or “redness” can vary from mild to severe (color of oxygenated red blood)	17, 18, 19, 20
		Gingivitis***	Mucosal fiber damage causes smooth/inflamed gingival surface, in contrast to the dimpled or stippled appearance of normal gingivae. Entire width of the attached gingivae will be erythematous	
Mucositis***	Inflammation of mucous membrane			
Pain***				

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Organ/Sites	Evaluation	Clinical Manifestation	Description of Clinical Manifestation	Photo Atlas
Lungs	<p>Clinical examination</p> <ul style="list-style-type: none"> • Chest auscultation • Pulse oximetry <p>Diagnostic testing</p> <ul style="list-style-type: none"> • Pulmonary function testing • Arterial blood gas • High-resolution CT of chest • Bronchoalveolar lavage (BAL) • Lung biopsy • Sputum for culture <p>Patient-reported symptoms and signs</p> <ul style="list-style-type: none"> • Difficulty breathing • Wheezing • Shortness of breath at rest and/or with exertion • Dry cough 	<p>Bronchiolitis obliterans*</p> <p>Bronchiolitis obliterans organizing pneumonia (BOOP)**</p>	<p>The new onset of an obstructive lung defect with air trapping confirmed by CT scan and pulmonary function testing or biopsy-proven bronchiolitis obliterans</p> <p>Inflammation of the bronchioles and surrounding tissue in the lungs</p>	

Organ/Sites	Evaluation	Clinical Manifestation	Description of Clinical Manifestation	Photo Atlas
Muscles, fascia, joints	Clinical examination <ul style="list-style-type: none"> • Palpation for areas of thickening, tightening, shortening of muscles or fascia; muscle tenderness • Evaluate range of motion • Muscle strength testing • Inspection for signs of edema or peau d'orange skin changes • Visual inspection for grooving, ridging Diagnostic testing <ul style="list-style-type: none"> • Creatine kinase • Aldolase • MRI for evidence of fasciitis • Electromyography Patient-reported symptoms and signs <ul style="list-style-type: none"> • Muscle cramps • Muscle pain • Muscle weakness • Joint stiffness • Restricted range of motion • Tightened muscles, tendons and fascia • Contractures 	Fasciitis	Stiffness, restricted range of motion	9
		Joint stiffness or contractures (secondary to sclerosis)		
		Myositis or polymyositis*	Evaluate with electromyography and measurement of creatine phosphokinase and aldolase	
		Edema**	Present in extremities, with or without erythema and peau d'orange skin	15
		Muscle cramps**	May be present with increased muscle enzymes	
Arthralgia or arthritis**	Uncommon, occasionally associated with the presence of autoantibodies			

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Organ/Sites	Evaluation	Clinical Manifestation	Description of Clinical Manifestation	Photo Atlas
GI tract	Clinical examination <ul style="list-style-type: none"> Examination of mouth and hypopharynx Diagnostic testing <ul style="list-style-type: none"> Endoscopy Barium contrast radiograph Swallowing study Stool test for fecal fat Biopsy Amylase Lipase Patient-reported symptoms and signs <ul style="list-style-type: none"> Anorexia Nausea Vomiting Abdominal pain Diarrhea Bloating Cramping Weight loss Painful swallowing Difficulty swallowing dry foods/pills 	Esophageal web	Smooth, circumferential ring of squamous mucosa; documented by endoscopy or barium contrast radiograph	
		Esophageal strictures or stenosis	Narrowing of the upper to mid third of the esophagus; documented by endoscopy or barium contrast radiograph	
		Pancreatic exocrine insufficiency**	Inability to properly digest food due to a lack of digestive enzymes; often improves with enzyme supplementation	
		Anorexia***		
		Nausea***		
		Vomiting***		
Diarrhea***				
Weight loss***				
Failure to thrive (infants and children)***				

Organ/Sites	Evaluation	Clinical Manifestation	Description of Clinical Manifestation	Photo Atlas
Liver	<p>Clinical examination</p> <ul style="list-style-type: none"> Assess for hepatomegaly and right upper quadrant abdominal tenderness <p>Diagnostic testing</p> <ul style="list-style-type: none"> Total and direct bilirubin Alkaline phosphatase ALT: Alanine aminotransferase AST: Aspartate aminotransferase GGT: Gamma glutamyl transpeptidase 5'-NT: 5' Nucleotidase Liver biopsy is required to confirm GVHD involvement of the liver <p>Patient-reported symptoms and signs</p> <ul style="list-style-type: none"> Jaundice Malaise Itching Fatigue 	Cholestasis*	The flow of bile from the liver is blocked; documented by increased bilirubin or alkaline phosphate	
		Acute hepatitis*		
Genitalia	<p>Clinical examination</p> <ul style="list-style-type: none"> Visual inspection of genitalia Pelvic exam <p>Diagnostic testing</p> <ul style="list-style-type: none"> Biopsy <p>Patient-reported symptoms and signs</p> <ul style="list-style-type: none"> Itching Painful intercourse Dryness Painful urination Burning 	Lichen planus-like features	Erythematous/violaceous tissue changes	
		Vaginal scarring and stenosis	A narrowing of the vagina, often with accompanying tissue changes such as dryness, loss of elasticity and resilience, adhesion and scar tissue	
		Fissures*	A break or slit in tissue typically appearing at the junction of skin and mucous membrane	
		Erosions*	Localized destruction or loss of the epidermis	
		Ulcers*	Localized destruction or loss below the epidermis	

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Organ/Sites	Evaluation	Clinical Manifestation	Description of Clinical Manifestation	Photo Atlas
Hematopoietic/immune	Clinical examination N/A Diagnostic testing <ul style="list-style-type: none"> • Complete blood count and differential • Test for presence of autoantibodies • Quantitative immunoglobulin levels Patient-reported symptoms and signs N/A	Thrombocytopenia**	Persistent decrease in the number of blood platelets; <100,000/ μ L	
		Eosinophilia**	Abnormal increase in the number of eosinophils; >500/ μ L	
		Lymphopenia**	Reduction in the number of lymphocytes; <500/ μ L	
		Hypo- or hypergammaglobulinemia**	Deficiency or excess of gamma globulins in the peripheral blood	
		Autoantibodies**	Autoimmune hemolytic anemia (AIHA) Idiopathic thrombocytopenic purpura (ITP) Autoantibodies may develop, including antinuclear antibody, anti-centromere antibody, anti-mitochondrial antibody, anti-ENA screen, anti-double stranded DNA antibody, anticardiolipin antibody	
Other	For these manifestations, chronic GVHD is often a diagnosis of exclusion	Pericardial or pleural effusions** Ascites** Peripheral neuropathy** Nephrotic syndrome** Myasthenia gravis** Cardiac conduction abnormality or cardiomyopathy**	Although these manifestations cannot be used to establish a diagnosis of chronic GVHD, a wide range of organ system manifestations including neurologic complications, nephrotic syndrome and cardiac abnormalities have been described in association with cGVHD and may represent cGVHD manifestations. If after careful differential diagnosis no alternative etiologic factor is identified, it may be concluded that these manifestations represent chronic GVHD disease activity.	

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A note on the distinction between acute and chronic GVHD

By classical definition, GVHD appearing before day 100 post-transplant is acute GVHD, and GVHD appearing after day 100 is chronic GVHD.

However, acute GVHD (maculopapular rash, nausea, vomiting, anorexia, profuse diarrhea, ileus or cholestatic hepatitis) may still occur later than 100 days post transplant (e.g., during tapering of

immunosuppressive drugs or following a donor lymphocyte infusion). Some patients may also develop overlap syndrome, where features of both acute and chronic GVHD are present. Community physicians will typically see transplant recipients well beyond 100 days post transplant, but it is still possible that a patient may be experiencing late-onset acute GVHD or overlap syndrome. Regardless, the treatment recommendation is the same: ***Collaborate with the transplant center to confirm the diagnosis and develop a treatment plan.***

Chronic GVHD Photo Atlas

This photo atlas contains pictorial representations of various clinical manifestations of chronic GVHD. Refer to the information in the preceding chart for a full description of all manifestations.



1. Poikiloderma

Hypo- and hyperpigmentary changes with erythema and atrophy.

See Chart page 3



2. Morphea-like

Localized patchy area(s) of moveable smooth or shiny skin with a leather-like waxy or hardened consistency. Note the fibrotic, hypopigmented area in the center of the plaque with a slightly hyperpigmented border. See Chart page 3



3. Keratosis pilaris

Skin-colored to erythematous perifollicular papules with spiny keratotic plugs within the follicular openings.

See Chart page 3



4. Lichen planus-like

Hyperpigmented/purple papules which may coalesce into annular (ring-like) small plaques. These lesions closely resemble the dermatologic disease lichen planus.

See Chart page 3



5. Lichen planus-like

Discrete to coalescent gray to white moveable papules or plaques.

See Chart page 3



6. Lichen sclerosus-like

Close-up showing "cigarette-paper" wrinkling. Lesions tend to be grouped in discrete patches.

See Chart page 3



7. Hyperpigmentation

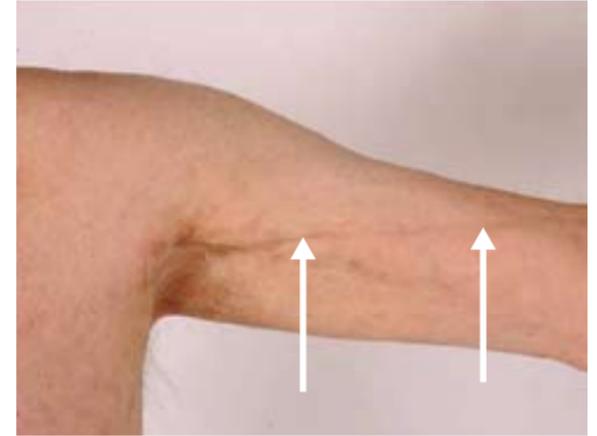
Excess pigmentation in the skin; may manifest in a widespread reticulated pattern.

See Chart page 4



8. Hypopigmentation, hyperpigmentation, sclerosis

Diminished (hypo-) or excess (hyper-) pigmentation in the skin. Sclerotic tissue is hard and fibrous, with a decreased ability to pinch. Superficial sclerosis is moveable upon palpation, while deep sclerosis is hidebound and fixed. See Chart page 3, 4



9. Sclerosis, fasciitis

Subcutaneous sclerosis/fasciitis can be detected by a "groove sign" seen here.

See Chart page 3



10. Sclerosis

Subcutaneous sclerosis can be manifested by rippling, dimpling of the skin and a resultant cellulite-like appearance.

See *Chart page 3*



11. Erosion

Localized tissue destruction characterized by complete or partial loss of only the epidermis.

See *Chart page 4*



12. Maculopapular

Raised and flat small, red lesions. Small scaly plaques.

See *Chart page 3*



13. Nail dystrophy

Longitudinal ridging, splitting, or brittle features of nails. Note periungual erythema.

See *Chart page 5*



14. Alopecia

Patchy alopecia is shown. May also include loss of body hair (after initial recovery of hair growth following chemotherapy or radiotherapy).

See *Chart page 5*



15. Edema

Edema in the extremities can be bilateral or unilateral (shown). May be present with erythema and peau d'orange skin. Edema may be associated as prodromal symptom to subcutaneous sclerosis and fasciitis.

See *Chart page 9*



16. Lichen planus

Lichenoid changes extending from the labial mucosa to the lip. Cheilosis (surface scaling and fissures in the corners of the mouth) is also present.

See Chart page 7



17. Mucocoeles

Numerous vesicle-like mucocoeles are seen along the center of the soft palate. Patchy white lichenoid hyperkeratosis and interspersed moderate erythematous changes are also evident across soft palate.

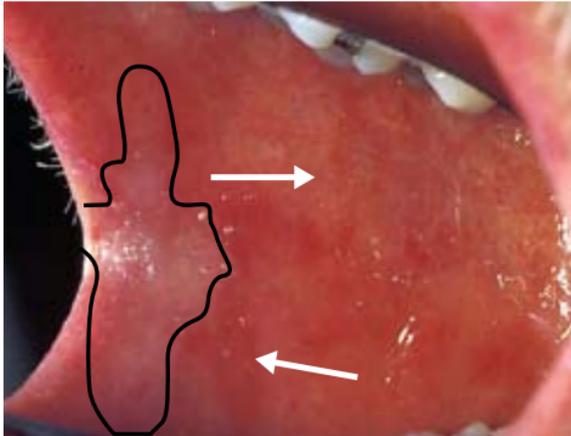
See Chart page 7



18. Erythema

Chapping and erythema of the vermilion lip. Erythema of labial mucosa.

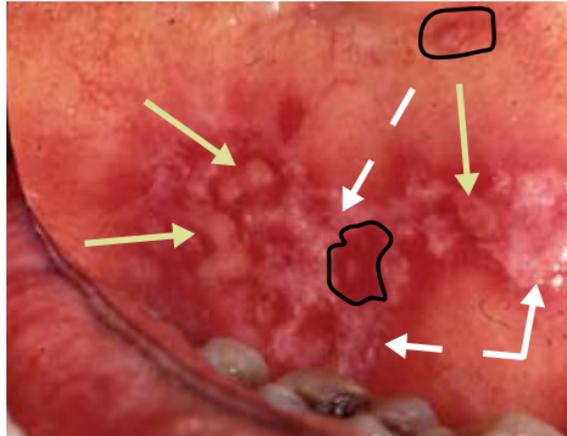
See Chart page 7



19. Erythema, hyperkeratinization

Patchy erythema (arrows) and sheet-like hyperkeratinization (black outline). Also note atrophy of buccal mucosal tissues.

See Chart page 7



20. Erythema, ulcerations, hyperkeratinization

Mixed pseudomembranous fibrin exudate (light green arrows). Lichenoid hyperkeratotic changes (dotted white arrows) involving the buccal mucosa. Erythema (black outline) surrounding pseudomembranous ulcerations.

See Chart page 7



21. Ulcerations

White patchy pseudomembranous ulcerations.
See Chart page 7



22. Keratoconjunctivitis sicca

Inadequate tear production (measured by Schirmer test) and conjunctival erythema. Also note scleral injection and chemosis (conjunctival edema).

See Chart page 6



23. Keratoconjunctivitis sicca

Note scleral injection and conjunctival erythema.

See Chart page 6



24. Blepharitis

Thickened, edematous and erythematous eyelid margins. Also note plugging of meibomian gland orifices (along the eyelid margin) and significant conjunctival hyperemia/injection.

See Chart page 6

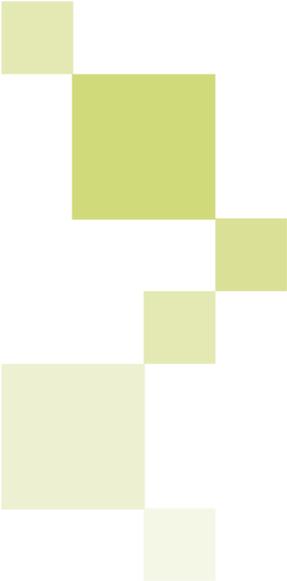


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References

¹Filipovich AH, Weisdorf D, Pavletic S, et al. National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: I. Diagnosis and Staging Working Group Report. *Biol Blood Marrow Transplant*. 2005; **11**(12): 945-956.

²Mitchell, S.A. and Pavletic, S.Z., *Measuring the therapeutic response in chronic GVHD trials: An instructional manual [CD]*. Silver Spring, Md.: Palladian Partners; 2006. Available online at www.asbmt.org/GVHD.

³These guidelines have been developed by the NMDP in consultation with Sandra A. Mitchell, CRNP, MScN, AOCN; National Institutes of Health Clinical Center; and Steven Z. Pavletic, M.D.; National Cancer Institute, National Institutes of Health, Bethesda, Md. The information in this document does not represent the official position of the NIH or the U.S. Government.

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For patient information on chronic GVHD, visit www.marrow.org/patient.

Disclaimer:

The purpose of this *Guide* is to outline general principles of hematopoietic cell transplantation and the care of transplant recipients. This *Guide* should not be used to replace the medical judgment or advice of an experienced physician.





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