

National Institutes of Health Chronic Graft-versus-Host Disease Consensus for Clinical Trials: I.  
The 2014 Diagnosis and Staging Working Group Report

Authors:

Affiliation:

Corresponding author:

Keywords: Chronic GVHD, NIH chronic GVHD, cGVHD diagnosis

Running title: Diagnosis and scoring of chronic Graft-versus-Host Disease

Abstract word count: 159

Manuscript word count: 6,001

Table: 2

Figure: 1

Supplemental Figure: 1

References: 46

## **Abstract**

The 2005 National Institute of Health (NIH) Consensus Conference proposed new criteria for diagnosis and scoring the severity of chronic GVHD. The 2014 NIH consensus maintains the framework of the prior consensus with further refinement based on new evidence. Revisions have been made to address areas of controversy or confusion, such as the overlap chronic GVHD subcategory and the distinction between active disease and past tissue damage. Diagnostic criteria for involvement of mouth, eyes, genitalia and lungs have been revised. Categories of chronic GVHD should be defined in ways that indicate prognosis, guide treatment, and define eligibility for clinical trials. Revisions have been made to focus attention on the causes of organ-specific abnormalities. If the entire abnormality can be unequivocally explained by a non-GVHD documented cause, the organ should be categorized as not affected by GVHD. This paradigm shift provides greater specificity, more accurately measures the global burden of disease attributed to GVHD, and will facilitate biomarker association studies.

## **Background**

Chronic graft-versus-host disease (GVHD) remains a serious and common complication of allogeneic hematopoietic cell transplantation (HCT), occurring in 30% to 70% of patients<sup>1</sup>. Chronic GVHD is a syndrome of variable clinical features resembling autoimmune and other immunologic disorders that occur later after HCT such as scleroderma, Sjögren syndrome, primary biliary cirrhosis, wasting syndrome, bronchiolitis obliterans, immune cytopenias, and chronic immunodeficiency<sup>2;3</sup>. The pathophysiology of the chronic GVHD syndrome may involve inflammation, cell mediated immunity, humoral immunity and fibrosis. Clinical manifestations nearly always presents during in the first year after transplantation, but some cases develop many years after HCT. Manifestations of chronic GVHD may be restricted to a single organ or site or may be widespread, with profound impact on quality of life. Other cases are self-limited and either smolder or resolve without immunosuppressive therapy.

Diagnosing and scoring the severity of chronic GVHD may be challenging for several reasons: limited understanding of the pathophysiology, coexistence of acute GVHD manifestations and, lack of biomarkers for the diagnosis and assessment of disease activity.

Overall risk profiles for acute GVHD and for chronic GVHD diagnosed per 2005 NIH consensus criteria<sup>4</sup> were similar in a large comparative study<sup>5</sup>. Of interest, risk factors associated with chronic GVHD were not changed after adjustment for prior acute GVHD, suggesting that chronic GVHD is not simply an evolution of preceding acute GVHD<sup>5</sup>.

Several retrospective and large prospective studies have validated many aspects of the 2005 NIH Chronic GVHD Diagnosis and Staging Consensus criteria<sup>4</sup> including organ scoring, global severity and GVHD categories<sup>6-20</sup>. Although, these criteria represents advancement in the field, many questions remain, including their role in clinical practice, clinical trials biomarker

discovery, and for regulatory review of new drugs or devices seeking FDA approval. For certain organs and sites, the minimal criteria to diagnose chronic GVHD have not been clearly defined. Other unresolved issues of the 2005 Consensus criteria include confusion about the chronic GVHD subcategories (especially the overlap GVHD), the rules for scoring abnormalities (symptoms, signs, diagnostic testing) not due to GVHD and lack of distinction between active disease and fixed deficit resulting from past tissue damage<sup>6;21</sup>.

The 2014 international NIH Chronic GVHD Diagnosis and Scoring Consensus Working Group that contributed to this document were subdivided into organ specific subgroups. Each subgroup reviewed all new evidence since 2005 and was asked to address controversies and unmet needs<sup>21</sup>. Their findings were reviewed by all the members of the working group and the steering committee and agreed upon, to establish the 2014 consensus criteria.

### **Purpose of this document**

The goals of this consensus document are to revise the 2005 NIH chronic GVHD consensus criteria<sup>4</sup> based on available evidence, to (a) clarify controversies related to the minimal criteria needed to establish the diagnosis in clinical practice; and (b) refine the definition of GVHD subcategories and organ severity scoring. The changes proposed in this document will help to characterize the various phenotypes of chronic GVHD at initial diagnosis and during the subsequent evolution of the disease for the purpose of clinical trials and biomarkers studies needed to advance the field. A summary of the 2005 NIH Chronic GVHD Diagnosis and Scoring Consensus Recommendations is shown in the Supplement Table.

## **Summary of recommendations that are new from the 2005 Consensus<sup>4</sup>**

1. Chronic GVHD subcategories (overlap and classic) have been removed.
  
2. Diagnostic criteria for organ system involvement have been modified as follows:
  - a. Mouth: Hyperkeratotic plaques have been removed as a diagnostic feature.
  
  - b. Eyes: Evaluation by an ophthalmologist is recommended for eye-specific clinical trials. Schirmer's test has been removed from the severity scoring form.
  
  - c. Genitalia: Signs and symptoms for male have been added and diagnostic criteria for female have been modified.
  
  - d. Lungs: Bronchiolitis obliterans syndrome (BOS) diagnostic criteria have been modified to enhance sensitivity. BOS that meets the new criteria for lung manifestation and lung biopsy confirming BO are now each defined as diagnostic features.
  
3. Organ-specific severity scoring has been modified as follows (Figure 1):
  - a. Skin: The composite score has been split into two scores to separate the extent of skin involvement (body surface area - BSA) from the specific skin features. Clinical features to be considered in the skin scores have been clarified and rules for the final skin scoring have been added and for calculation of global severity.

- b. Mouth: Asymptomatic lichen planus-like features (score 0) has been incorporated.
- c. Eye: Kerato-conjunctivitis sicca (KCS) confirmed by an ophthalmologist in an asymptomatic patient (score 0) is now captured. Scoring regarding eye drops criterion is clarified to include only lubricant drops.
- d. Genitalia: New criteria are proposed for scoring severity based on signs as an exploratory measure.
- e. Lungs: The lung function score which included both FEV1 and DLCO has been simplified to include only the FEV1, thus increasing specificity. Rules for final lung scoring have been modified to enhance specificity and for calculation of global severity.
- f. Joint: Photographic image-based range of motion (P-ROM)<sup>22</sup> has been added to the joint assessment as an exploratory measure.
- g. Other indicators have been simplified such as removal of progressive onset, cardiac conduction defects and coronary artery involvement (Figure 1).
- h. Attributions of abnormalities not due to GVHD have been incorporated in the organ-specific scoring.

4. The evaluator's opinion regarding overall severity and the changes from previous evaluation has been added to the scoring form (Figure 1).

### **Diagnosis of chronic GVHD**

Clinical features determine whether the clinical syndrome of GVHD is considered acute or chronic, not time after transplantation<sup>4</sup>. In the 2005 consensus criteria, the simultaneous presence of acute GVHD features in patients with chronic GVHD was classified as overlap GVHD<sup>4</sup>. Overlap GVHD has been a subject of controversy and confusion (see Differential Diagnosis between Acute and Chronic GVHD in the following section). The overlap GVHD subcategory has been associated with worse survival compared to the “classic” subcategory (absence of acute GVHD features) of chronic GVHD<sup>9;13;20;23</sup>, but not in all studies<sup>7;18</sup>. Based on current knowledge and in light of controversy related to the overlap subcategory, the 2014 consensus criteria have removed the overlap GVHD, while still recommending documentation of all clinical features in patients with chronic GVHD that, are relevant for prognostication, treatment guidance, response assessment, biomarker studies and clinical trials.

Throughout this document, *diagnostic* signs and symptoms refer to those manifestations that establish the presence of chronic GVHD without need for further testing or evidence of other organ involvement. *Distinctive* signs and symptoms of chronic GVHD refer to those manifestations that are not ordinarily found in acute GVHD but are not considered sufficient in isolation to establish an unequivocal diagnosis of chronic GVHD. Additional testing such as a biopsy documenting histological features of chronic GVHD or the presence of distinctive features in another site is needed to establish the diagnosis of chronic GVHD. *Other features or unclassified entities* of chronic GVHD define the rare, controversial, or non-specific features of

chronic GVHD that cannot be used to establish the diagnosis of chronic GVHD. *Common* signs and symptoms of chronic GVHD refer to manifestations found in both chronic and acute GVHD (Table 1).

Characteristics of the clinical features that establish the diagnosis of chronic GVHD might not serve as the most appropriate parameters for assessing severity of chronic GVHD. Valid and reliable diagnostic criteria might not be sufficiently sensitive to change to be useful as treatment-response criteria. Conversely, a sensitive measure of chronic GVHD response might not necessarily serve as an appropriate diagnostic and scoring tool.

The Working Group recommends that the diagnosis of chronic GVHD require at least one diagnostic manifestation of chronic GVHD or at least one distinctive manifestation, with the later confirmed by pertinent biopsy, laboratory tests, evaluation by a specialist (ophthalmologist, gynecologist) or radiology in the same or other organ, unless stated otherwise. As in acute GVHD, infection and other causes may confound or complicate the differential diagnosis of chronic GVHD and must be excluded (e.g., nail dystrophy due to onychomycosis, herpes simplex or *Candida albicans* infections of the oral cavity, drug toxicity). Diagnostic and distinctive features of chronic GVHD can be found in the skin and appendages, mouth, eyes, genitalia, esophagus, lungs, and connective tissues. Biopsy or other testing is always encouraged and often valuable to confirm the presence of chronic GVHD, but is not always feasible and is not mandatory if the patient has at least one of the diagnostic findings of chronic GVHD (Table 1). An in-depth discussion of recommended terminology for histopathology interpretation may be found in a forthcoming histopathology working group report. A biopsy read as “consistent with” or “unequivocal” chronic GVHD should be considered sufficient to establish the diagnosis of chronic GVHD if accompanied by at least one distinctive clinical manifestation.

## **Organ-specific manifestations of chronic GVHD**

In all cases, drug reaction, infection, recurrent or new malignancy and other causes must be excluded. Diagnostic clinical or laboratory features sufficient for the diagnosis of chronic GVHD are italicized in the sections below.

### **Skin**

Diagnostic clinical features include *poikiloderma* (e.g., atrophy, pigmentary changes and telangiectasia), *lichen planus-like eruption* (e.g., erythematous/violaceous flat topped papules or plaques with or without surface reticulations or a silvery or shiny appearance ), *deep sclerotic features* (e.g., smooth, waxy, indurated skin - “thickened or tight skin”, caused by deep and diffuse sclerosis over a wide area generally causing limitation of joint mobility), *morphea-like superficial sclerotic features* (e.g., localized patchy areas of moveable smooth or shiny skin, leathery-like consistency, often with dyspigmentation) or as *lichen sclerosus-like lesions* (e.g., discrete to coalescent gray to white moveable papules or plaques, often with follicular plugs, shiny appearance, and cigarette paper-like wrinkled texture). Severe sclerotic features characterized by thickened, tight, and fragile skin are often associated with poor wound-healing, inadequate lymphatic drainage, and skin ulcers from minor trauma.

Depigmentation and papulosquamous lesion are “distinctive” features of chronic GVHD (i.e., not seen in acute GVHD, but not sufficiently unique to be considered diagnostic of chronic GVHD). These features contribute to the diagnosis of chronic GVHD in combination with biopsy or laboratory confirmation of GVHD in skin or another organ. Sweat impairment and intolerance to temperature change from loss of sweat glands are seen in chronic GVHD, and are

considered in the “other” feature category along with other manifestations such as ichthyosis, keratosis pilaris, hypopigmentation and hyperpigmentation (Table 1). These “other” features cannot be used to establish the initial diagnosis of chronic GVHD. Skin manifestations found in both acute and chronic GVHD include erythema, maculopapular rash and pruritus are categorized as “common” features. The presence of one or more of the “common” features (without a diagnostic criterion in another organ) cannot be used to establish the initial diagnosis of chronic GVHD.

Assessment of extent and severity of skin chronic GVHD is complex because some clinical features may reflect past ‘damage’ (hypo- and hyper- pigmentary changes) or sequelae of long-standing fibrosis (i.e., fixed joint contractures after several years of deep sclerosis). Assessment of disease activity is difficult in patients with poikiloderma (atrophic skin, hyperpigmentation, hypopigmentation and telangiectasia) when smoldering ill-defined erythema is admixed with pigmentary changes. Pigmentary change alone (seen in poikiloderma, or more commonly as simple post-inflammatory pigmentary change and not representing active GVHD) is *not* included in the percentage of BSA skin score calculation (See Table 1/Figure 1). Erythema, a “common” feature, is included in the BSA skin score calculation as it generally represents inflammation associated with active GVHD.

## **Nails**

Dystrophy consisting of longitudinal ridging, nail splitting or brittleness, onycholysis, pterygium unguis, and nail loss (usually symmetric and affecting most nails) are distinctive signs of chronic GVHD.

## **Hair**

Distinctive features of chronic GVHD include new scarring or nonscarring scalp alopecia (not due to chemotherapy or radiotherapy) and loss of body hair. Other characteristics seen with chronic GVHD include premature graying, thinning, or brittleness.

## **Mouth**

Diagnostic features of oral chronic GVHD include *lichen planus-like changes*, characterized by hyperkeratotic white lines and lacy-appearing lesions and plaque-like changes affecting the oral mucosa. Changes are typically observed in the buccal mucosa and tongue, although all intraoral surfaces and the vermilion lip may be involved. These diagnostic white changes may be observed with or without associated erythema or ulcerations, which are not considered “diagnostic” features. The presence of isolated hyperkeratotic plaques without lichen planus-like changes, so called leukoplakia is no longer considered a diagnostic criterion, since these lesions should be considered a distinct clinical entity that may imply malignant potential. Decreased range of motion of the jaw secondary to skin sclerosis should be assessed according to skin criteria, and is no longer considered as diagnostic criterion in the oral section. Distinctive features of chronic GVHD include xerostomia (dryness), mucoceles, mucosal atrophy, ulcers and pseudomembranes, but infectious pathogens such as yeast or herpes virus, and secondary malignancy must be excluded. Manifestations common to both acute and chronic GVHD include gingivitis, mucositis, erythema and pain. Figure 1 details the scoring and incorporates asymptomatic oral chronic GVHD as a diagnostic feature.

## Eyes

Distinctive manifestations of chronic GVHD include new onset of dry, "gritty", or painful eyes, cicatricial conjunctivitis, keratoconjunctivitis sicca (KCS) and confluent areas of punctate keratopathy. Other features include photophobia, periorbital hyperpigmentation, and blepharitis (erythema of the eye lids with edema, telangiectasias of lid margin). New ocular sicca documented by low Schirmer's test with a mean value of  $\leq 5$  mm at 5 minutes (preferably with confirmation of normal value at an established baseline) or a new onset of keratoconjunctivitis sicca by slit lamp exam with mean Schirmer test values of 6 to 10 mm (preferably with confirmation of normal values at an established baseline) is sufficient for the diagnosis of chronic GVHD if accompanied by distinctive manifestations in at least one other organ. Patients with ocular symptoms prior to transplant should be evaluated by an ophthalmologist for assessment of ocular surface including presence of KCS, conjunctival scarring and inflammation. Baseline evaluation post-transplant approximately day 100 is strongly encouraged. Figure 1 details the scoring and incorporates asymptomatic ocular chronic GVHD. The scoring of ocular involvement includes the number of times an individual has to use lubricant eye drops each day. The international consensus guidelines on ocular GVHD, have proposed a more detailed scoring schema which involves comprehensive ophthalmological evaluation including pre-transplant evaluation<sup>24</sup>. These remain to be validated and should be considered in clinical trials addressing ocular involvement. Schirmer's test may be useful for diagnosis of ocular GVHD, but is not useful for follow-up of ocular GVHD due to poor correlation with symptom change<sup>15</sup>. For this reason, Schirmer's test has been removed from the scoring form in the current recommendation (Figure 1).

## **Genitalia**

Chronic GVHD of the genital tract (female and male) is often associated with oral chronic GVHD<sup>25</sup>. Diagnostic features of genitalia chronic GVHD include *lichen planus-like features, lichen sclerosus-like features, vaginal scarring, clitoral/labial agglutination (females), phimosis and urethral/meatus scarring or stenosis (males)*.

Genital examination is recommended, even in asymptomatic patients (female and male), especially if signs of chronic GVHD are present in the mouth. If a gynecologist is unavailable, external examination may be performed, but, in this instance, vaginal scarring may be missed.

*Female genitalia:* The vulva and vagina may be affected by chronic GVHD. Symptoms may include dryness, burning, pruritus, pain to touch, dysuria and dyspareunia either with penile insertion or deep penetration leading to sexual dysfunction. Signs of genital chronic GVHD may include patchy or generalized erythema, tenderness on cotton tipped applicator palpation of vestibular gland openings or vulvar mucosa, mucosal erosions or fissures, lace-like leukokeratosis, labial resorption, labial fusion or clitoral hood agglutination, fibrinous vaginal adhesions, circumferential fibrous vaginal banding, vaginal shortening, synechiae, dense sclerotic changes, and complete vaginal stenosis<sup>25-29</sup>.

*Male genitalia:* Manifestations of chronic GVHD may be under recognized and underreported in men. The glans penis and the urethra or meatus may be affected. Patients may report painful sexual intercourse, and a burning sensation. Genital signs of GVHD include non-infectious balanoposthitis, lichen sclerosis-like or lichen planus-like features, phimosis or urethra or meatus scarring or stenosis<sup>30</sup>.

## **Gastrointestinal tract (GI)**

Diagnostic features include *esophageal web, stricture, or concentric rings* documented by endoscopy, or barium contrast radiograph. Chronic GVHD may be associated with pancreatic atrophy and exocrine insufficiency leading to malabsorption which often improves with oral pancreatic enzyme supplementation. Manifestations common to both acute and chronic GVHD include anorexia, nausea, vomiting, diarrhea, weight loss, and failure to thrive. These symptoms can be due to non-GVHD causes such as drug side effect, motility disorders or infections. Wasting syndrome may be a manifestation of chronic GVHD but is often multifactorial (e.g., decreased caloric intake, poor intestinal absorption of macronutrients, increased resting energy expenditures and hypercatabolism). Unintentional weight loss occurring over a three month period should be documented irrespective of causality in clinical trials, unless definitive causality other than GVHD is identified. Endoscopic findings of gastrointestinal mucosal edema and erythema or focal erosions with histologic changes of apoptotic epithelial cells and crypt cell dropout are manifestations of acute but not chronic GVHD. An in-depth discussion of recommended terminology for histopathology interpretation may be found in a forthcoming histopathology working group report. Patients with unresolved acute GVHD may have more severe intestinal mucosal lesions including ulcers and mucosal sloughing.

## **Liver**

There are no liver manifestations that are either distinctive or diagnostic of chronic GVHD. Liver GVHD can also be accompanied by clinical manifestations of acute GVHD, with or without manifestations of chronic GVHD. Other potential causes of liver disease occurring more than day 100 after HCT, include viral infections, biliary obstruction, drug toxicity, and other less

common disorders. GVHD after day 100 can present in two ways. One resembles acute hepatitis (steeply rising serum ALT, with or without jaundice or stable transaminitis), almost always after tapering of immunosuppressive drugs or after donor lymphocyte infusion (DLI). This presentation requires a prompt diagnosis, and often necessitates a liver biopsy in the absence of chronic GVHD in other organ. The other resembles a slowly progressive cholestatic disorder with elevation of serum alkaline phosphatase and gamma-glutamyl transpeptidase, followed by jaundice. Acute hepatitis and progressive cholestatic features are included in the “common” category. The liver has no clinical features in the “other” category.

## **Lungs**

Historically, the only diagnostic pulmonary manifestation of chronic GVHD was biopsy-proven bronchiolitis obliterans (*BO*). However, because biopsy is invasive and associated with risk of bleeding and other complications, experts now endorse the diagnosis of bronchiolitis obliterans syndrome (BOS) using pulmonary functions testing (PFT)<sup>31;32</sup>. BOS is characterized by the new onset of an obstructive lung defect. Clinical manifestations may include dyspnea on exertion, cough or wheezing; however patients are often asymptomatic early in the disease process. Pneumothorax, pneumomediastinum or subcutaneous emphysema are rare and often represent advanced disease. Restrictive pulmonary function abnormalities are not characteristics of BOS but may reflect extra-pulmonary restriction (leading to false reduction of FEV1), secondary to advanced sclerotic GVHD of the chest wall, myositis or other intrapulmonary processes not related to GVHD, such as cryptogenic organizing pneumonia or pulmonary fibrosis. Further investigation beyond simple pulmonary testing is needed to evaluate these complex problems.

*Bronchiolitis Obliterans Syndrome* (BOS) is a diagnostic feature of lung chronic GVHD

when all of the following criteria are met:

- (1)  $FEV1/VC < 0.7$  or the 5<sup>th</sup> percentile of predicted.
  - a. FEV1= Forced Expiratory Volume in 1 second.
  - b. VC= Vital Capacity (Forced Vital Capacity “FVC” or Slow Vital Capacity “SVC”, whichever is greater).
  - c. The 5<sup>th</sup> percentile of predicted is equivalent to the lower value of predicted confidence interval.
  - d. For pediatric patients or elderly populations, use  $<$  predicted confidence interval using NHANESIII calculations<sup>33</sup>
- (2)  $\%FEV1 < 75\%$  of predicted with  $\geq 10\%$  decline over less than 2 years.  $\%FEV1$  should not correct to  $> 75\%$  with albuterol and the rate of decline for the corrected values should still remain at  $\geq 10\%$  decline over 2 years.
- (3) Absence of infection in the respiratory tract, documented with investigations directed by clinical symptoms, such as radiologic studies (radiographs or computed tomographic scans) or microbiologic cultures (sinus aspiration, upper respiratory tract viral screen, sputum culture, bronchoalveolar lavage).
- (4) Either one distinctive manifestation of chronic GVHD or another supporting feature of BOS (see below).

The following criteria support the diagnosis of BOS:

- Evidence of air trapping by expiratory CT or small airway thickening or bronchiectasis by high-resolution chest computed tomography.

- Evidence of air trapping by PFTs: RV > 120% (Residual Volume) or RV/TLC > 120% predicted (RV/Total Lung Capacity).

The current recommended work-up for BOS includes PFT testing and expiratory CT.

Because a new diagnostic technique termed parametric response mapping is currently under investigation, a high resolution (helical) CT of inspiration and expiration is encouraged if available. This technique will permit visual representation of lung affected by obstructive disease (BOS) versus lung tissue with normal aeration or restrictive disease and may become a valuable measure in the future<sup>34</sup>.

Other entities that are currently not diagnostic or distinctive of lung chronic GVHD, but remain areas of active investigation include: (1) cryptogenic organizing pneumonia (COP) (formerly known as bronchiolitis obliterans organizing pneumonia), and (2) progressive restrictive lung disease (in the absence of extra pulmonary causes). These unclassified entities have been placed in the “other” category in Table 1. There are no “common” pulmonary features of GVHD.

## **Musculoskeletal system**

Diagnostic features include *fascial involvement* often affecting the forearms or legs and often associated with sclerosis of the overlying skin and subcutaneous tissue. Fascial involvement may develop without overlying sclerotic changes of the skin, and can result in *joint stiffness or contractures* when present near joints. Early fasciitis may present with pain and swelling with or without erythema. *Fasciitis* is detected on examination by stiffness, restricted range of motion (e.g., often decreased dorsal wrist flexion or inability to assume a Buddha prayer posture), edema of extremities with or without erythema (early sign), peau d’orange (edematous skin with

prominent pores resembling the surface of an orange) or *joint contractures* (late complications). Clinical myositis with muscle tenderness and elevated muscle enzymes concentration in the blood is a distinctive but non-diagnostic manifestation of chronic GVHD. Myositis may present as proximal myopathy, but this complication is rare and does not explain the frequent complaints of severe cramps. Evaluation of myositis includes electromyography and measurement of creatine phosphokinase or aldolase. Arthralgia and “true” arthritis are uncommon and are occasionally associated with the presence of autoantibodies.

### **Hematopoietic and immune systems**

Hematopoietic and immunological abnormalities are frequently associated with chronic GVHD but cannot be used to establish the diagnosis of chronic GVHD. Cytopenias may result from stromal damage or autoimmune processes. Lymphopenia ( $\leq 500/\mu\text{l}$ ), eosinophilia ( $\geq 500/\mu\text{l}$ ), hypogammaglobulinemia or hypergammaglobulinemia may be present. Autoantibodies may develop with autoimmune hemolytic anemia and idiopathic thrombocytopenic purpura. Thrombocytopenia ( $< 100,000/\mu\text{l}$ ) at the time of chronic GVHD diagnosis has been associated with a poor prognosis.

### **Other findings**

Serositis (pericardial or pleural effusions or ascites), peripheral neuropathy, myasthenia gravis, nephrotic syndrome, membranous glomerulonephritis, Raynaud phenomenon and cardiac involvement have been attributed to chronic GVHD, but these manifestations are rare. For these entities, attribution to chronic GVHD is often a diagnosis of exclusion.

## Differential Diagnosis between Acute and Chronic GVHD

As in the 2005 consensus criteria, the 2014 consensus recognizes two main categories of GVHD (acute and chronic). The broad category of acute GVHD includes (1) classic acute GVHD (erythema, maculopapular rash, nausea, vomiting, anorexia, profuse diarrhea, ileus or cholestatic liver disease) occurring within 100 days after transplantation or DLI (without diagnostic or distinctive signs of chronic GVHD) and (2) persistent, recurrent or late acute GVHD: features of classic acute GVHD without diagnostic or distinctive manifestations of chronic GVHD occurring beyond 100 days of transplantation or DLI (often seen during the taper or after withdrawal of immune suppression).

In the 2005 criteria, the broad category of chronic GVHD included (1) classic chronic GVHD without features characteristic of acute GVHD and (2) an overlap syndrome where features of chronic and acute GVHD appear together. The 2014 consensus criteria have removed the subcategories of chronic GVHD for several reasons as discussed here. Overlap subcategory is transient, often depends on the degree of immunosuppression, and is subject to changes during the disease course. Many patients who present with “overlap” chronic GVHD resolve the acute features while other disease features persist. Similarly patients with classic chronic GVHD may develop acute GVHD features when immunosuppression is tapered. The “overlap” GVHD subcategory has been associated with worse survival in some <sup>9;13;19;20;23</sup>, but not all publications. Hyperbilirubinemia and small intestinal/colonic involvement are known risk factors for increased mortality in chronic GVHD patients (reviewed in <sup>2;7;35;36</sup>). For these reasons overlap GVHD has been removed as a separate entity. Instead, the 2014 international consensus recommends that the use of “overlap” syndrome for prognostic purpose should be replaced by the specific clinical feature abnormalities that confer increased risk.

In the absence of features fulfilling the definition of chronic GVHD, the persistence, recurrence or new onset of characteristic skin, gastrointestinal tract or liver abnormalities should be classified as acute GVHD regardless of the time after transplantation. With appropriate stratification, however, patients with persistent, recurrent or late acute GVHD may be included in clinical trials together with patients who have NIH chronic GVHD<sup>5</sup>.

### **Clinical Scoring of Organ Systems**

Modifications have been made to the 2005 consensus organ scoring system based on available evidence, or lack thereof, and to address concerns raised by investigators and in clinical practice<sup>21</sup>. Figure 1 shows the consensus scoring system for individual organs. Several considerations explain the selection of the features for the proposed scoring system versus the response criteria discussed in a separate article. (1) Scoring criteria are intended for baseline or cross-sectional use, while response criteria are intended for longitudinal evaluation in therapeutic trials. (2) In general, scoring measures have been designed so that they can be easily performed by general practitioners (non-transplant physician and nurses). Two organ systems, eyes and female genitalia (Supplemental Figure 1) are best assessed by an organ-specific consultant. By design, the only required laboratory testing needed to complete the scoring table is measurement of liver tests. Lung scoring is preferentially determined by pulmonary function test, when available, but symptoms may be substituted if PFTs is not available. (3) The broad scoring categories help to classify patients and provide immediate, clinically meaningful information summarizing the disease extent and severity. (4) The scoring system does not attempt to distinguish between disease activity (inflammation and apoptosis or target cells) and fixed anatomic deficits from past tissue injury, but now incorporates the attribution of abnormalities

not due to chronic GVHD. (5) In organ systems, with two possible scores (e.g. skin) the higher score is used for calculating global severity. FEV1 obtained from pulmonary function test (PFT) supersedes the clinical scoring in lung. (6) Sites or organ with unequivocal documentation of attribution other than GVHD cannot be evaluated and are not scored in computing the overall severity, but the data are incorporated in the scoring form (Figure 1). For example, 12.5% BSA skin rash entirely due to varicella zoster is scored as 0 for skin, shortness of breath after walking on flat ground due to lobar pneumonia is scored 0 for lung, FEV1 of 60% is scored 0 if is unchanged from the pre-transplant FEV1 value). We anticipate that patients will often have multifactorial etiologies to explain the abnormality present (e.g. shortness of breath in a patient with established BOS and now with worsening FEV1 due to superimposed viral bronchiolitis). In these instances, the abnormality is scored as if the entire deficit is due to GVHD. This inherent limitation of the scoring system is unavoidable.

Organ sites considered for scoring include skin, mouth, eyes, gastrointestinal tract, liver, lungs, joints and fascia, and the genital tract. Each organ or site is scored according to a 4-point scale (0-3) with 0 representing no involvement and 3 reflecting severe impairment. In addition, performance status is captured on a 0 to 3 scale, and check boxes note the presence or absence of other specific manifestations.

The current consensus document proposes changes to the 2005 consensus scoring system for some organs as follows (Figure 1):

1. Skin: The composite score is now split into two scores to document the extent of skin involvement (BSA) and the specific skin features separately. Clinical features to be considered in the skin scores have been clarified. The higher of the two scores is to be used for computation of the global severity.

2. Mouth: Lichen planus-like features in asymptomatic patients (score 0) are now incorporate.
3. Eye: Keratoconjunctivitis sicca (KCS) confirmed by an ophthalmologist in an asymptomatic patient (score 0) is now incorporated Scoring regarding the requirement of eye drops is clarified to include only lubricant drops. Schirmer's test has been removed from the scoring form.
4. Genitalia: Scoring is now based on severity of the signs instead of symptoms, based on limited available data<sup>25;26;30</sup> and opinion of experts (supplemental Figure 1 represents an exploratory measure to be completed by specialist or trained practitioners). Female genital GVHD is not scored if a gynecologist is unable to examine the patient.
5. Liver: Scoring is based on increments in values for total serum bilirubin and alanine aminotransferase (ALT).
6. Lungs: Lung function score, which used both FEV1 and DLCO, was simplified to FEV1 values alone, thus improving specificity. The rule for the final lung scoring has been changed such that the FEV1 score should be used in cases with discrepancy between symptoms and FEV1 scores.
7. Joint: Photographic-range of motion (P-ROM)<sup>22</sup> has been added to joint assessment as an exploratory measure and should not be included in the calculation of global severity (Figure 1).
8. Other indicators, clinical manifestations or complications related to chronic GVHD have been simplified. These include the removal of progressive onset, cardiac conduction defects and coronary artery involvement.

The form shown in Figure 1 should be completed based on an assessment of current status without consideration of past manifestations. Abnormalities with unequivocal causes other than GVHD are annotated in scoring each organ or site. This change will help to address some of the controversies and confusion raised by investigators<sup>21</sup>. Furthermore, identification of abnormalities not due to GVHD will help in the selection of patients for biomarker studies of chronic GVHD and clinical trials. We realize that abnormality may have a multifactorial etiology. In those instances, the organ should be scored if the entire abnormality is due to GVHD.

### **Global Scoring of Chronic GVHD**

The fundamentals of the global scoring of chronic GVHD remain unchanged from 2005 NIH consensus criteria<sup>4</sup>. Several studies have shown that the 2005 NIH global severity score baseline predicts overall survival and non-relapse mortality<sup>11;18;37;38</sup> and some elements of the score have been validated with patient reported quality of life measures<sup>10</sup>.

Eight organ sites (skin, eyes, gastrointestinal tract, liver, lungs, joint and fasciae, and genital tract) are considered for calculating global score. Elements included in the proposed global scoring include both the number of organs or sites involved and the severity score within each affected organ. Performance status scoring is not incorporated into the global scoring system. The global descriptions of mild, moderate, and severe were chosen to reflect the degree of organ impact and functional impairment due to chronic GVHD. Although scoring is often used at the time of initial diagnosis, evaluating the clinical score periodically during the course of chronic GVHD may revise prognostic expectations and better describe the current severity of chronic GVHD. The global scoring system can be applied only after the diagnosis of chronic GVHD is

confirmed by either (1) presence of a diagnostic feature or, if a diagnostic feature is not present, (2) at least one distinctive manifestation of chronic GVHD with the diagnosis supported by histologic, radiologic or laboratory evidence of GVHD from any site or by a distinctive clinical manifestation in another site. Table 2 outlines the computation of the chronic GVHD global severity scoring which is categorized as mild, moderate or severe.

The current consensus incorporates asymptomatic organ manifestation (e.g. asymptomatic oral chronic GVHD). These do not affect the global scoring of chronic GVHD, since the recorded score is still 0. Attribution of abnormalities to causes other than chronic GVHD could have an impact in the global scoring. For instance, if a patient has a score of  $\geq 1$  in an organ and if the abnormality is explained entirely and unequivocally by a non-GVHD cause, the organ is scored as zero. The capture of the potential confounders in the organ scoring (attribution due to other causes than chronic GVHD) will correct any overestimation of organ involvement<sup>11;37</sup> and improve the specificity of the scoring system. These changes are supported by the results of a recent prospective study evaluating the impact of cofounders in the organ scoring and in the global severity of chronic GVHD, and showed that approximately 40% of abnormalities in at least one organ were unequivocally explained to causes other than chronic GVHD resulting in a modest downgrade of global severity after the confounder was taken into account<sup>39</sup>. As outlined previously, if the abnormality in an organ is multifactorial, the organ is scored as if the entire deficit is due to GVHD.

### **Indications for systemic therapy**

Symptomatic mild chronic GVHD may often be managed with local therapies alone (e.g. topical corticosteroids for the skin involvement). In patients with chronic GVHD that involves

three or more organs or with a score of 2 or greater in any single organ, however, systemic immunosuppressive therapy should be considered. In some organ sites (mouth, eyes, genital tract), aggressive local therapy alone may be reasonable, as response to systemic therapy may be suboptimal or may not warrant the risk. Co-morbidly infections may also modify decisions regarding the time and intensity of therapy. Good medical practice and judgment dictate flexibility in this recommendation. Comprehensive monitoring for early detection of insidious disease progression in other sites is mandatory when management relies entirely on local therapy. Early intervention with effective systemic therapy can prevent progression to severe chronic GVHD. Effective immune modulating therapy can ameliorate clinical manifestations and prolong survival. In patients with newly diagnosed chronic GVHD who are already receiving immune suppressive medications, the dosage may be increased or other agents can be added. Chronic GVHD itself and systemic immunosuppressive therapy, both impair immune defenses. Therefore patients should receive infection-prevention measures as outlined in the forthcoming Ancillary Therapy and Supportive Care working group document.

### **Assessment of risk of transplant related mortality (TRM)**

Chronic GVHD is one of the major causes of late TRM after allogeneic HCT. Prospective studies using the 2005 criteria have shown that the skin score, lung score and gastrointestinal score each predict the risk of TRM<sup>8;10;16;37</sup>. Previous studies have identified several factors associated with an increased risk of TRM among patients with chronic GVHD including, involvement of multiple organs or sites, decreased clinical performance score, thrombocytopenia (platelet count <100,000/ $\mu$ L) at the time of diagnosis, progressive onset of chronic GVHD from prior acute GVHD (or steroid dose at onset of chronic GVHD),

hyperbilirubinemia and a higher percentage of skin involvement at the time of diagnosis, and others<sup>5;14;35;40-46</sup>. The characteristics consistently associated with an increased risk of late TRM among patients with chronic GVHD are thrombocytopenia and progressive onset of chronic GVHD from acute GVHD.

The consensus guidelines for assessment of chronic GVHD severity summarized in this document can be used in making decisions about treatment and enrollment in clinical trials. The goals of treatment for chronic GVHD are to relieve symptoms, control disease activity and prevent damage and disability. As a general rule, the intensity of treatment should be calibrated to the extent and severity of disease manifestations. Patients with mild or asymptomatic manifestations limited to a single organ or site can often be managed with close observation or topical treatment, or by slowing the taper of prophylactic immunosuppressive treatment. Those with more severe manifestations or involvement of multiple organs or sites typically require systemic treatment. Although it is commonly assumed that systemic treatment might improve survival, previous randomized trials have not demonstrated such a benefit, and some studies have shown statistically significant differences or trends indicating worse survival with intensive immunosuppressive treatment. Therefore, chronic GVHD should be managed with the lowest amount of treatment needed to control the disease until immunological tolerance eventually emerges. Therapeutic interventions that facilitate tolerance induction remain an unmet clinical need.

## References

1. Lee SJ, Flowers MED. Recognizing and managing chronic graft-versus-host disease. In: Gewirtz AM, Muchmore EA, Burns LJ, eds. Hematology 2008: American Society of Hematology Education Program Book. Washington, DC: American Society of Hematology; 2008:134-141.
2. Lee SJ, Vogelsang G, Flowers MED. Chronic graft-versus-host disease. Biol Blood Marrow Transplant 2003;9:215-233.
3. Flowers MED, Vogelsang GB. Clinical manifestations and natural history. In: Vogelsang GB, Pavletic SZ, eds. Chronic Graft Versus Host Disease: Interdisciplinary Management. New York, NY: Cambridge University Press; 2009:56-69.
4. Filipovich 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;11:945-956.
5. Flowers MED, Inamoto Y, Carpenter PA et al. Comparative analysis of risk factors for acute graft-versus-host disease and for chronic graft-versus-host disease according to National Institutes of Health consensus criteria. Blood 2011;117:3214-3219.
6. Baird K, Steinberg SM, Grkovic L et al. National Institutes of Health chronic graft-versus-host disease staging in severely affected patients: organ and global scoring correlate with established indicators of disease severity and prognosis. Biol.Blood.Marrow.Transplant. 2013;19:632-639.
7. Vigorito AC, Campregher PV, Storer BE et al. Evaluation of NIH consensus criteria for classification of late acute and chronic GVHD. Blood 2009;114:702-708.

8. Jacobsohn DA, Kurland BF, Pidala J et al. Correlation between NIH composite skin score, patient reported skin score, and outcome: results from the Chronic GVHD Consortium. *Blood* 2012;120:2545-2552.
9. Pidala J, Vogelsang G, Martin P et al. Overlap subtype of chronic graft-versus-host disease is associated with an adverse prognosis, functional impairment, and inferior patient-reported outcomes: a Chronic Graft-versus-Host Disease Consortium study. *Haematologica* 2012;97:451-458.
10. Pidala J, Kurland B, Chai X et al. Patient-reported quality of life is associated with severity of chronic graft-versus-host disease as measured by NIH criteria: report on baseline data from the Chronic GVHD Consortium. *Blood* 2011;117:4651-4657.
11. Arai S, Jagasia M, Storer B et al. Global and organ-specific chronic graft-versus-host disease severity according to the 2005 NIH Consensus Criteria. *Blood* 2011;118:4242-4249.
12. Pidala J, Kurland BF, Chai X et al. Sensitivity of changes in chronic graft-versus-host disease activity to changes in patient-reported quality of life: results from the Chronic Graft-versus-Host Disease Consortium. *Haematologica* 2011;96:1528-1535.
13. Arora M, Pidala J, Cutler CS et al. Impact of prior acute GVHD on chronic GVHD outcomes: a chronic graft versus host disease consortium study. *Leukemia* 2013;27:1196-1201.
14. Kuzmina Z, Eder S, Bohm A et al. Significantly worse survival of patients with NIH-defined chronic graft-versus-host disease and thrombocytopenia or progressive onset type: results of a prospective study. *Leukemia* 2012;26:746-756.
15. Inamoto Y, Chai X, Kurland BF et al. Validation of measurement scales in ocular graft-versus-host disease. *Ophthalmology* 2012;119:487-493.

16. Pidala J, Chai X, Kurland BF et al. Analysis of gastrointestinal and hepatic chronic graft-versus-host disease manifestations on major outcomes: a Chronic Graft-Versus-Host Disease Consortium study. *Biol.Blood.Marrow.Transplant.* 2013;19:784-791.
17. Jagasia MH, Abonour R, Long GD et al. Palifermin for the reduction of acute GVHD: a randomized, double-blind, placebo-controlled trial. *Bone Marrow Transplant.* 2012;47:1350-1355.
18. Cho B-S, Min C-K, Eom K-S et al. Feasibility of NIH consensus criteria for chronic graft-versus-host disease. *Leukemia* 2009;23:78-84.
19. Arora M, Nagaraj S, Witte J et al. New classification of chronic GVHD: added clarity from the consensus diagnoses. *Bone Marrow Transplant.* 2009;43:149-153.
20. Pérez-Simón JA, Encinas C, Silva F et al. Prognostic factors of chronic graft-versus-host disease following allogeneic peripheral blood stem cell transplantation: the National Institutes Health Scale plus the type of onset can predict survival rates and the duration of immunosuppressive therapy. *Biol Blood Marrow Transplant* 2008;14:1163-1171.
21. Inamoto Y, Jagasia M, Wood WA et al. Investigator feedback about the 2005 NIH diagnostic and scoring criteria for chronic GVHD. *Bone Marrow Transplant.* 2014;49:532-538.
22. Inamoto Y, Pidala J, Chai X et al. Assessment of joint and fascia manifestations in chronic graft-versus-host disease. *Arthritis and Rheumatology* 2014;66:1044-1052.
23. Jagasia M, Giglia J, Chinratanalab W et al. Incidence and outcome of chronic graft-versus-host disease using National Institutes of Health consensus criteria. *Biol.Blood.Marrow.Transplant.* 2007;13:1207-1215.

24. Ogawa Y, Kim SK, Dana R et al. International Chronic Ocular Graft-vs-Host-Disease (GVHD) Consensus Group: proposed diagnostic criteria for chronic GVHD (Part I). *Science Reporter* 2013;3:3419.
25. Zantomio D, Grigg AP, Macgregor L et al. Female genital tract graft-versus-host disease: incidence, risk factors and recommendations for management. *Bone Marrow Transplant.* 2006;38:567-572.
26. Smith Knutsson E, Björk Y, Broman AK et al. Genital chronic graft-versus-host disease in females: a cross-sectional study. *Biol Blood Marrow Transplant* 2014;20:806-11.
27. Hirsch P, Leclerc M, Rybojad M et al. Female genital chronic graft-versus-host disease: importance of early diagnosis to avoid severe complications. *Transplantation* 2012;93:1265-1269.
28. Spinelli S, Chiodi S, Costantini S et al. Female genital tract graft-versus-host disease following allogeneic bone marrow transplantation. *Haematologica* 2003;88:1163-1168.
29. Shanis D, Merideth M, Pulanic TK et al. Female long-term survivors after allogeneic hematopoietic stem cell transplantation: evaluation and management (Review). *Semin.Hematol.* 2012;49:83-93.
30. Mueller SM, Haeusermann P, Rovo A et al. Genital chronic GVHD in men after hematopoietic stem cell transplantation: a single-center cross-sectional analysis of 155 patients. *Biol.Blood.Marrow.Transplant.* 2013;19:1574-1580.
31. Williams KM, Chien JW, Gladwin MT, Pavletic SZ. Bronchiolitis obliterans after allogeneic hematopoietic stem cell transplantation. *JAMA* 2009;302:306-314.
32. Hildebrandt GC, Fazekas T, Lawitschka A et al. Diagnosis and treatment of pulmonary chronic GVHD: report from the consensus conference on clinical practice in chronic GVHD (Review). *Bone Marrow Transplant.* 2011;46:1283-1295.

33. Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. *American Journal of Respiratory & Critical Care Medicine* 1999;159:179-187.
34. Gálban CJ, Han MK, Boes JL et al. Computed tomography-based biomarker provides unique signature for diagnosis of COPD phenotypes and disease progression. *Nat.Med.* 2012;18:1711-1715.
35. Arora M, Klein JP, Weisdorf DJ et al. Chronic GVHD risk score: a Center for International Blood and Marrow Transplant Research analysis. *Blood* 2011;117:6714-6720.
36. Inamoto Y, Storer BE, Lee SJ et al. Failure-free survival after second-line systemic treatment of chronic graft-versus-host disease. *Blood* 2013;121:2340-2346.
37. Palmer J, Williams K, Inamoto Y et al. Pulmonary symptoms measured by the National Institutes of Health lung score predict overall survival, nonrelapse mortality, and patient-reported outcomes in chronic graft-versus-host disease. *Biol Blood Marrow Transplant* 2014;20:337-344.
38. Pidala J, Chai X, Martin P et al. Hand grip strength and 2-minute walk test in chronic graft-versus-host disease assessment: analysis from the Chronic GVHD Consortium. *Biol.Blood.Marrow.Transplant.* 2013;19:967-972.
39. Aki SZ, Inamoto Y, Storer BE et al. Confounding factors affecting the National Institutes of Health (NIH) chronic GVHD organ-specific score and global severity [abstract]. *Biol Blood Marrow Transplant* 2014;20:S265-S266.
40. Jacobsohn DA, Arora M, Klein JP et al. Risk factors associated with increased nonrelapse mortality and with poor overall survival in children with chronic graft-versus-host disease. *Blood* 2011;118:4472-4479.

41. Lee SJ, Klein JP, Barrett AJ et al. Severity of chronic graft-versus-host disease: association with treatment-related mortality and relapse. *Blood* 2002;100:406-414.
42. Pavletic SZ, Carter SL, Kernan NA et al. Influence of T-cell depletion on chronic graft-versus-host disease: results of a multicenter randomized trial in unrelated marrow donor transplantation. *Blood* 2005;106:3308-3313.
43. Akpek G, Lee SJ, Flowers ME et al. Performance of a new clinical grading system for chronic graft-versus-host disease: a multi-center study. *Blood* 2003;102:802-809.
44. Stewart BL, Storer B, Storek J et al. Duration of immunosuppressive treatment for chronic graft-versus-host disease. *Blood* 2004;104:3501-3506.
45. Sullivan KM, Witherspoon RP, Storb R et al. Prednisone and azathioprine compared with prednisone and placebo for treatment of chronic graft-versus-host disease: Prognostic influence of prolonged thrombocytopenia after allogeneic marrow transplantation. *Blood* 1988;72:546-554.
46. Wingard JR, Piantadosi S, Vogelsang GB et al. Predictors of death from chronic graft versus host disease after bone marrow transplantation. *Blood* 1989;74:1428-1435.

Table 1. Signs and symptoms of chronic GVHD

<b>ORGAN OR SITE</b>	<b>DIAGNOSTIC</b> <i>(Sufficient to establish the diagnosis of chronic GVHD)</i>	<b>DISTINCTIVE</b> <i>(Seen in chronic GVHD, but insufficient alone to establish a diagnosis of chronic GVHD)</i>	<b>OTHER FEATURES OR UNCLASSIFIED ENTITIES*</b>	<b>COMMON</b> <i>(Seen with both acute and chronic GVHD)</i>
Skin	<ul style="list-style-type: none"> <li>• Poikiloderma</li> <li>• Lichen planus-like features</li> <li>• Sclerotic features</li> <li>• Morphea-like features</li> <li>• Lichen sclerosus-like features</li> </ul>	<ul style="list-style-type: none"> <li>• Depigmentation</li> <li>• Papulosquamous lesions</li> </ul>	<ul style="list-style-type: none"> <li>• Sweat impairment</li> <li>• Ichthyosis</li> <li>• Keratosis pilaris</li> <li>• Hypopigmentation</li> <li>• Hyperpigmentation</li> </ul>	<ul style="list-style-type: none"> <li>• Erythema</li> <li>• Maculopapular rash</li> <li>• Pruritus</li> </ul>
Nails		<ul style="list-style-type: none"> <li>• Dystrophy</li> <li>• Longitudinal ridging, splitting or brittle features</li> <li>• Onycholysis</li> <li>• Pterygium unguis</li> <li>• Nail loss** (usually symmetric, affects most nails)</li> </ul>		
Scalp and Body Hair		<ul style="list-style-type: none"> <li>• New onset of scarring or non-scarring scalp alopecia, (after recovery from chemoradiotherapy)</li> <li>• Scaling.</li> </ul>	<ul style="list-style-type: none"> <li>• Thinning scalp hair, typically patchy, coarse or dull (not explained by endocrine or other causes),</li> <li>• Premature gray hair</li> </ul>	
Mouth	<ul style="list-style-type: none"> <li>• Lichen planus-like changes</li> </ul>	<ul style="list-style-type: none"> <li>• Xerostomia</li> <li>• Mucoceles</li> <li>• Mucosal atrophy</li> <li>• Ulcers and Pseudomembranes **</li> </ul>		<ul style="list-style-type: none"> <li>• Gingivitis</li> <li>• Mucositis</li> <li>• Erythema</li> <li>• Pain</li> </ul>
Eyes		<ul style="list-style-type: none"> <li>• New onset dry, gritty, or painful eyes</li> <li>• Cicatricial conjunctivitis</li> <li>• Keratoconjunctivitis sicca</li> <li>• Confluent areas of punctate keratopathy</li> </ul>	<ul style="list-style-type: none"> <li>• Photophobia</li> <li>• Periorbital hyperpigmentation</li> <li>• Blepharitis (erythema of the eye lids with edema)</li> </ul>	
<b>Genitalia</b>	<ul style="list-style-type: none"> <li>• <b>Lichen planus-like features</b></li> <li>• <b>Lichen sclerosus-like features</b></li> </ul>	<ul style="list-style-type: none"> <li>• <b>Erosions**</b></li> <li>• <b>Fissures**</b></li> <li>• <b>Ulcers**</b></li> </ul>		
<b>Females</b>	<ul style="list-style-type: none"> <li>• <b>Vaginal scarring or clitoral/labial agglutination</b></li> </ul>			
<b>Males</b>	<ul style="list-style-type: none"> <li>• <b>Phymosis or urethral/meatus scarring or stenosis</b></li> </ul>			

<b>ORGAN OR SITE</b>	<b>DIAGNOSTIC</b> <i>(Sufficient to establish the diagnosis of chronic GVHD)</i>	<b>DISTINCTIVE</b> <i>(Seen in chronic, but insufficient alone to establish a diagnosis of chronic GVHD)</i>	<b>OTHER FEATURES OR UNCLASSIFIED ENTITIES<sup>†</sup></b>	<b>COMMON</b> <i>(Seen with both acute and chronic GVHD)</i>
GI Tract	<ul style="list-style-type: none"> <li>• Esophageal web</li> <li>• Strictures or stenosis in the upper to mid third of the esophagus**</li> </ul>		<ul style="list-style-type: none"> <li>• Exocrine pancreatic insufficiency</li> </ul>	<ul style="list-style-type: none"> <li>• Anorexia</li> <li>• Nausea</li> <li>• Vomiting</li> <li>• Diarrhea</li> <li>• Weight loss</li> <li>• Failure to thrive (infants and children)</li> </ul>
Liver				<ul style="list-style-type: none"> <li>• Total bilirubin, alkaline phosphatase &gt; 2 x upper limit of normal</li> <li>• ALT &gt; 2x upper limit of normal<sup>†</sup></li> </ul>
Lung	<ul style="list-style-type: none"> <li>• Bronchiolitis obliterans diagnosed with lung biopsy</li> <li>• Bronchiolitis obliterans syndrome</li> </ul>	<ul style="list-style-type: none"> <li>• Air trapping and bronchiectasis on chest CT</li> </ul>	<ul style="list-style-type: none"> <li><sup>†</sup> Cryptogenic organizing pneumonia (COP)</li> <li><sup>†</sup> Restrictive lung disease</li> </ul>	
Muscles, Fascia, Joints	<ul style="list-style-type: none"> <li>• Fasciitis</li> <li>• Joint stiffness or contractures secondary to sclerosis</li> </ul>	<ul style="list-style-type: none"> <li>• Myositis or polymyositis <sup>††</sup></li> </ul>	<ul style="list-style-type: none"> <li>• Edema</li> <li>• Muscle cramps</li> <li>• Arthralgia or arthritis</li> </ul>	
Hematopoietic and Immune			<ul style="list-style-type: none"> <li>• Thrombocytopenia</li> <li>• Eosinophilia</li> <li>• Lymphopenia</li> <li>• Hypo- or hyper-gammaglobulinemia</li> <li>• Autoantibodies (AIHA, ITP)</li> <li>• Raynaud's phenomenon</li> </ul>	
Other			<ul style="list-style-type: none"> <li>• Pericardial or pleural effusions</li> <li>• Ascites</li> <li>• Peripheral neuropathy</li> <li>• Nephrotic syndrome</li> <li>• Myasthenia gravis</li> <li>• Cardiac conduction abnormality or cardiomyopathy</li> </ul>	

\*Can be acknowledged as part of the chronic GVHD symptomatology if diagnosis is confirmed

\*\*In all cases, infection, drug effect, malignancy or other causes must be excluded.

<sup>†</sup> Pulmonary entities under investigation or unclassified.

†† Diagnosis of chronic GVHD requires biopsy

Abbreviation: ALT (alanine aminotransferase); AST (aspartate aminotransferase); PFTs (pulmonary function tests); AIHA (autoimmune hemolytic anemia); ITP (idiopathic thrombocytopenic purpura).

**Table 2 - NIH Global Severity of Chronic GVHD**

**Mild chronic GVHD**

1 or 2 organs involved (not lung) *plus*  
Score in involved organs 1 *plus*  
Lung score 0

**Moderate chronic GVHD**

3 or more organs involved *plus*  
Score of 1 in each organ

OR

At least 1 organ (not lung) with a score of 2

OR

Lung score 1

**Severe chronic GVHD**

At least 1 organ with a score of 3

OR

Lung score of 2 or 3

**Key points:**

1. In skin: higher of the two scores to be used for calculating global severity.
2. In lung: FEV1 is used instead of clinical score for calculating global severity.
3. If a non-GVHD documented cause unequivocally explains the entire organ abnormality, then the organ is not scored for global severity. If the abnormality is thought to be multifactorial, it is scored without attribution from non-GVHD causes.

**Figure 1. Organ Scoring of Chronic GVHD**

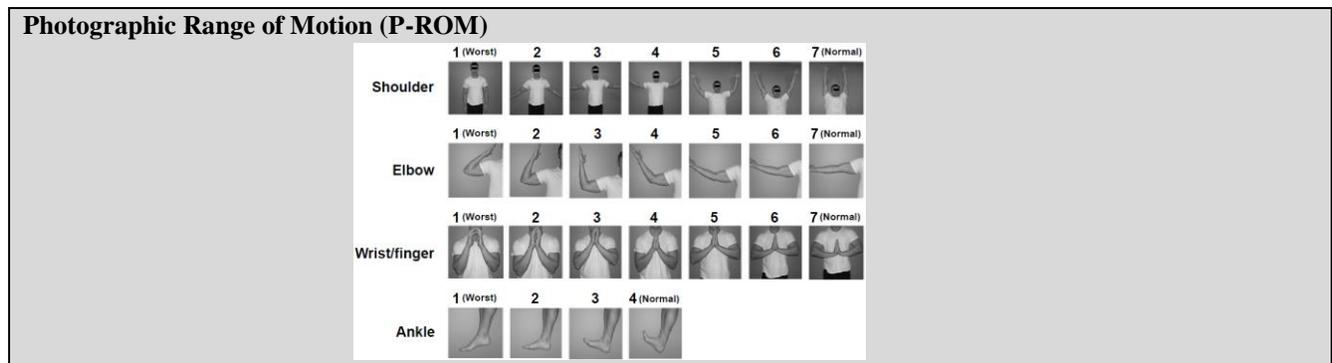
	SCORE 0	SCORE 1	SCORE 2	SCORE 3
<b>PERFORMANCE</b> <b>SCORE:</b> <input type="text"/> <b>KPS ECOG LPS</b>	<input type="checkbox"/> Asymptomatic and fully active (ECOG 0; KPS or LPS 100%)	<input type="checkbox"/> Symptomatic, fully ambulatory, restricted only in physically strenuous activity (ECOG 1, KPS or LPS 80-90%)	<input type="checkbox"/> Symptomatic, ambulatory, capable of self-care, >50% of waking hours out of bed (ECOG 2, KPS or LPS 60-70%)	<input type="checkbox"/> Symptomatic, limited self-care, >50% of waking hours in bed (ECOG 3-4, KPS or LPS <60%)
<b>SKIN†</b> <b>SCORE % BSA</b> <input type="text"/> <u>GVHD features to be scored by BSA:</u> <b>Check all that applies:</b> <input type="checkbox"/> Maculopapular rash/erythema <input type="checkbox"/> Lichen planus-like features <input type="checkbox"/> Sclerotic features <input type="checkbox"/> Papulosquamous lesions or ichthyosis <input type="checkbox"/> Keratosis pilaris-like GVHD	<input type="checkbox"/> No BSA involved	<input type="checkbox"/> 1-18% BSA	<input type="checkbox"/> 19-50% BSA	<input type="checkbox"/> >50% BSA
<b>SKIN FEATURES</b> <b>SCORE:</b>	<input type="checkbox"/> No sclerotic features		<input type="checkbox"/> Superficial sclerotic features “not hidebound” (able to pinch)	<b>Check all that applies:</b> <input type="checkbox"/> Deep sclerotic features <input type="checkbox"/> “Hidebound” (unable to pinch) <input type="checkbox"/> Impaired mobility <input type="checkbox"/> Ulceration
<u>Other skin GVHD features (NOT scored by BSA)</u> <b>Check all that applies:</b> <input type="checkbox"/> Hyperpigmentation <input type="checkbox"/> Hypopigmentation <input type="checkbox"/> Poikiloderma <input type="checkbox"/> Severe or generalized pruritus <input type="checkbox"/> Hair involvement <input type="checkbox"/> Nail involvement <input type="checkbox"/> Abnormality present but explained entirely by non-GVHD documented cause (specify): _____				
<b>MOUTH</b> <u>Lichen planus-like features present:</u> <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Abnormality present but explained entirely by non-GVHD documented cause (specify): _____	<input type="checkbox"/> No symptoms	<input type="checkbox"/> Mild symptoms <b>with</b> disease signs but not limiting oral intake significantly	<input type="checkbox"/> Moderate symptoms with disease signs <b>with</b> partial limitation of oral intake	<input type="checkbox"/> Severe symptoms with disease signs on examination <b>with</b> major limitation of oral intake

**Figure 1. Organ Scoring of Chronic GVHD (continued)**

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
<b>EYES</b>	<input type="checkbox"/> No symptoms	<input type="checkbox"/> Mild dry eye symptoms not affecting ADL (requirement of lubricant eye drops $\leq 3$ x per day)	<input type="checkbox"/> Moderate dry eye symptoms partially affecting ADL (requiring lubricant eye drops $> 3$ x per day or punctal plugs), <b>WITHOUT</b> new vision impairment due to KCS	<input type="checkbox"/> Severe dry eye symptoms significantly affecting ADL (special eyewear to relieve pain) <b>OR</b> unable to work because of ocular symptoms <b>OR</b> loss of vision due to KCS
<i>Keratoconjunctivitis sicca (KCS) confirmed by Ophthalmologist:</i>	<input type="checkbox"/> Yes <input type="checkbox"/> No			
<input type="checkbox"/> Abnormality present but explained entirely by non-GVHD documented cause (specify): _____				
<b>GI Tract</b>	<input type="checkbox"/> No symptoms	<input type="checkbox"/> Symptoms without significant weight loss* ( $<5\%$ )	<input type="checkbox"/> Symptoms associated with mild to moderate weight loss* (5-15%)	<input type="checkbox"/> Symptoms associated with significant weight loss* $>15\%$ , requires nutritional supplement for most calorie needs or esophageal dilation
<b>Check all that applies:</b>				
<input type="checkbox"/> Esophageal web/proximal stricture or ring				
<input type="checkbox"/> Dysphagia				
<input type="checkbox"/> Anorexia				
<input type="checkbox"/> Nausea				
<input type="checkbox"/> Vomiting				
<input type="checkbox"/> Diarrhea				
<input type="checkbox"/> Weight loss*				
<input type="checkbox"/> Failure to thrive				
<input type="checkbox"/> Abnormality present but explained entirely by non-GVHD documented cause (specify): _____				
<b>LIVER</b>	<input type="checkbox"/> Normal total bilirubin and ALT $< 2$ x NUL	<input type="checkbox"/> Normal total bilirubin and ALT $\geq 2$ x NUL	<input type="checkbox"/> Elevated total Bilirubin but $\leq 3$ mg/dL NUL	<input type="checkbox"/> Elevated total bilirubin $> 3$ x NUL
<input type="checkbox"/> Abnormality present but explained entirely by non-GVHD documented cause (specify): _____				
<b>LUNGS**</b>				
<b>Symptoms score:</b>	<input type="checkbox"/> No symptoms	<input type="checkbox"/> Mild symptoms (shortness of breath after climbing one flight of steps)	<input type="checkbox"/> Moderate symptoms (shortness of breath after walking on flat ground)	<input type="checkbox"/> Severe symptoms (shortness of breath at rest; requiring $O_2$ )
<b>Lung obstructive function score:</b>	<input type="checkbox"/> FEV1 $\geq 80\%$	<input type="checkbox"/> FEV1 60-79	<input type="checkbox"/> FEV1 40-59%	<input type="checkbox"/> FEV1 $\leq 39\%$
FEV1 <input type="text"/>				
<i>Pulmonary function tests</i>				
<input type="checkbox"/> Not performed				
<input type="checkbox"/> Abnormality present but explained entirely by non-GVHD documented cause (specify): _____				

**Figure 1. Organ scoring of chronic GVHD (continued)**

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
<b>JOINTS AND FASCIA</b>	<input type="checkbox"/> No symptoms	<input type="checkbox"/> Mild tightness of arms or legs, normal or mild decreased range of motion (ROM) <b>AND</b> not affecting ADL	<input type="checkbox"/> Tightness of arms or legs <b>OR</b> joint contractures, erythema thought due to fasciitis, moderate decrease ROM <b>AND</b> mild to moderate limitation of ADL	<input type="checkbox"/> Contractures <b>WITH</b> significant decrease of ROM <b>AND</b> significant limitation of ADL (unable to tie shoes, button shirts, dress self etc.)
<u>P-ROM score</u> (see below) Shoulder (1-7): ____ Elbow (1-7): ____ Wrist/finger (1-7): ____ Ankle (1-4): ____				
	<input type="checkbox"/> Abnormality present but explained entirely by non-GVHD documented cause (specify): _____			
<b>GENITAL TRACT</b> (See Supplemental table <sup>‡</sup> ) <b>Check all that applies</b>	<input type="checkbox"/> No signs	<input type="checkbox"/> Mild signs <sup>†</sup> and females with or without discomfort on exam	<input type="checkbox"/> Moderate signs <sup>†</sup> and may have signs* of discomfort on exam	<input type="checkbox"/> Severe signs <sup>†</sup> with or without symptoms
<input type="checkbox"/> Not examined				
Currently sexually active				
<input type="checkbox"/> Yes				
<input type="checkbox"/> No				
	<input type="checkbox"/> Abnormality present but explained entirely by non-GVHD documented cause (specify): _____			
<b><u>Other indicators, clinical features or complications related to chronic GVHD (check all that apply and assign a score to its severity (0-3) based on its functional impact where applicable none – 0, mild -1, moderate -2, severe – 3)</u></b>				
<input type="checkbox"/> Ascites (serositis) ____	<input type="checkbox"/> Myasthenia Gravis ____		<input type="checkbox"/> Eosinophilia > 500/ $\mu$ l ____	
<input type="checkbox"/> Pericardial Effusion ____	<input type="checkbox"/> Peripheral Neuropathy ____		<input type="checkbox"/> Platelets <100,000/ $\mu$ l ____	
<input type="checkbox"/> Pleural Effusion(s) ____	<input type="checkbox"/> Polymyositis ____		<input type="checkbox"/> Others (specify): _____	
<input type="checkbox"/> Nephrotic syndrome ____	<input type="checkbox"/> Weight loss* without GI symptoms			
<b>Overall GVHD Severity</b> (Opinion of the evaluator)	<input type="checkbox"/> No GVHD	<input type="checkbox"/> Mild	<input type="checkbox"/> Moderate	<input type="checkbox"/> Severe



† Skin scoring should use both percentage of BSA involved by disease signs and the cutaneous features scales. When a discrepancy exists between the percentage of total body surface (BSA) score and the skin feature score, **OR** if superficial sclerotic features are present (Score 2), but there is impaired mobility or ulceration (Score 3), the higher level should be used for the final skin scoring.

\* Weight loss within 3 months.

\*\*Lung scoring should be performed using both the symptoms and FEV1 scores whenever possible. FEV1 should be used in the final lung scoring where there is discrepancy between symptoms and FEV1 scores.

**Abbreviations:** ECOG (Eastern Cooperative Oncology Group), KPS (Karnofsky Performance Status), LPS (Lansky Performance Status); BSA (body surface area); ADL (activities of daily living); LFTs (liver function tests); AP (alkaline phosphatase); ALT (alanine aminotransferase); NUL (normal upper limit).

‡ To be completed by specialist or trained medical providers (see Supplemental Table).

## Supplement Figure 1 – Genital Tract Chronic Graft-versus-Host Assessment and Scoring Form

Name: \_\_\_\_\_ Date of birth: \_\_\_\_\_ Assessment date: \_\_\_\_\_

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
<b>GENITAL TRACT (male or female)</b>	<input type="checkbox"/> No signs	<input type="checkbox"/> Mild signs and females may have symptoms* WITH discomfort on exam	<input type="checkbox"/> Moderate signs and may have symptoms* with discomfort on exam	<input type="checkbox"/> Severe signs with or without symptoms*
Currently sexually active: <input type="checkbox"/> Yes <input type="checkbox"/> No <b><i>Check all signs that applies:</i></b> <input type="checkbox"/> Lichen planus-like features <input type="checkbox"/> Lichen sclerosis-like features <input type="checkbox"/> Vaginal scarring (female) <input type="checkbox"/> Clitoral/labial agglutination (female) <input type="checkbox"/> Labial resorption (female) <input type="checkbox"/> Erosions <input type="checkbox"/> Fissures <input type="checkbox"/> Ulcers <input type="checkbox"/> Phimosis (male) <input type="checkbox"/> Urethral meatus scarring/ stenosis (male) <input type="checkbox"/> Abnormality present but <b><i>NOT</i></b> thought to represent GVHD (specify cause): _____ <input type="checkbox"/> Abnormality thought to represent GVHD <b><i>PLUS</i></b> other causes(specify cause): _____				

\*Genital symptoms are not specific to cGVHD and can represent premature gonadal failure or genital tract infection.

**If a gynecologist is unavailable**, external examination may be performed to determine “discomfort on exam” as follows:

- Spread the labia majora to inspect the vulva for the above signs. Touch the vestibular gland openings (Skene’s and Bartholin’s), labia minora and majora gently with a qtip. Vulvar pain elicited by the gentle touch of a qtip is classified as discomfort on examination. Palpate the vaginal walls with a single digit to detect bands, shortening, narrowing or other signs of vaginal scarring.
- If the woman is sexually active, determine whether qtip palpation or gentle palpation of scarred ridges elicits pain similar to that which the woman experiences during intercourse.

**Female genitalia:** Severity of signs:

- Mild (any of the following); erythema on vulvar mucosal surfaces, vulvar lichen-planus or vulvar lichen-sclerosis
- Moderate (any of the following); erosive inflammatory changes of the vulvar mucosa, fissures in vulvar folds
- Severe (any of the following); labial fusion, clitoral hood agglutination, fibrinous vaginal adhesions, circumferential fibrous vaginal banding, vaginal shortening, synechia, dense sclerotic changes, and complete vaginal stenosis

**Male genitalia:** Diagnostic features include lichen planus-like or lichen sclerosis-like features and phimosis or urethral scarring or stenosis. Severity of signs: **Mild** – lichen planus-like feature; **Moderate** – lichen sclerosis-like feature or moderate erythema; **Severe** – phimosis or urethral/meatal scarring

Biopsy obtained: <input type="checkbox"/> Yes <input type="checkbox"/> No	Site biopsied: _____	GVHD confirmed by histology: <input type="checkbox"/> Yes <input type="checkbox"/> No
Change from previous evaluation: <input type="checkbox"/> No prior or current GVHD <input type="checkbox"/> Improved <input type="checkbox"/> Stable <input type="checkbox"/> Worse <input type="checkbox"/> N/A (baseline)		

Completed by (spell out name): \_\_\_\_\_ Date form completed: \_\_\_\_\_

## Supplemental Figure Legend

Figure 1. Poikilodermic chronic GVHD. Hypo- and hyperpigmentation with admixed erythema on the upper chest.

Figure 2. Lichen sclerosus-like chronic GVHD. Shiny skin and cigarette-paper-like wrinkling on the central back.

Figure 3. Subcutaneous sclerosis/fasciitis in chronic GVHD. Rippled and nodular induration of the subcutaneous tissue resembling eosinophilic fasciitis with range of motion restriction.

Figure 4. Morphea-like chronic GVHD. Well-demarcated sclerotic plaque with marked skin thickening and associated hair loss.

Figure 5. Lichen planus-like chronic GVHD. Reticulate erythematous papules and plaques with overlying silvery scale. Note the characteristic post-inflammatory pigmentation.

