National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: IIa. The 2020 Clinical Implementation and Early Diagnosis Working Group Report

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Abstract:

Recognition of the earliest signs and symptoms of chronic graft versus host disease (cGVHD) remains a challenge. The standardization provided by the National Institutes of Health 2005 and 2014 consensus projects have helped improve accuracy of both diagnosis and response for clinical trials, but utilization of these tools in day-to-day practice remains variable. Additionally, when patients meet these diagnostic criteria, many already have significant morbidity and possibly irreversible organ damage. The goals of this early diagnosis project are two fold. First, we provide consensus recommendations regarding implementation of the current diagnostic guidelines into routine transplant care, outside of clinical trials, which could potentially avoid late recognition of cGVHD. Second, we outline future research efforts to more accurately recognize cGVHD earlier, both globally as well as highly morbid organ-specific manifestions of cGVHD. Identification of early features of cGVHD that have high positive predictive value for progression to more severe manifestations of the disease could potentially allow for future pre-emptive clinical trials.

Introduction:

The field of allogeneic hematopoietic cell transplantation (HCT) has dramatically changed over the last decade due to practice changes, but the number of transplant procedures continues to increase. Despite prevention strategies such as T cell depletion and post-transplant cyclophosphamide which are associated with reduced rates of chronic graft-versus-host disease (cGVHD) as low as 10-15% in some studies,[1–4] most allogeneic HCT recipients still receive peripheral blood stem cell (PBSC) grafts and experience a 30-50% incidence of cGVHD.[5–7] This results in substantial long-term morbidity and mortality,[8,9] and has been shown to significantly impact the health status, health-related quality of life and return to social roles of affected HCT survivors.[10–14]

The National Institutes of Health (NIH) cGVHD Consensus projects in 2005[15,16] and 2014[17,18] provided the standardization of cGVHD diagnosis, severity and response criteria for clinical trials. Multiple publications have supported the validity of the NIH diagnostic criteria as well as the prognostic significance of the severity of the disease, and their use has allowed the development of better structured clinical trials, leading to a first ever FDA approval for cGVHD.[19] However, many patients do not meet NIH diagnostic criteria until irreversible manifestations of the disease (i.e. sicca symptoms, lung GVHD) have already developed. Therefore, there is an imperative need to recognize cGVHD at an earlier stage before the NIH diagnostic criteria are met and to develop pre-emptive interventions that can prevent progression to irreversible organ damage and avoid the need for systemic therapy.

Purpose:

Chronic GVHD is a pleomorphic disease with an often insidious beginning and disease course. While the current diagnostic and scoring criteria are well established, providers with less experience with cGVHD, such as primary oncology providers who resume the care of patients after HCT, may not recognize the earliest symptoms and signs of cGVHD.[20] Patient education regarding early signs and symptoms of cGVHD and utilization of better communication practices from patient and/or primary oncogist to the transplant center could avoid late diagnosis. We make several recommendations based on input from disease experts to improve the recognition of cGVHD using the current NIH guidelines in routine clinical care which can be used at transplant centers as well as by referring oncologists and primary care providers.

Despite the validity and usefulness of the current NIH guidelines, it is also recognized that patients may have concerning signs and symptoms for a period of time prior to meeting formal NIH diagnostic criteria. Therefore, the second main goal of this working group was to review approaches allowing earlier diagnosis of cGVHD before irreversible changes in organ function have occured. Future clinical trials could use these early diagnostic tools as eligibility criteria in clinical trials testing if pre-emptive treatment strategies are feasible and effective. As examples, we discuss three organs associated with a high incidence of irreversibility and morbidity; skin/fascia, eyes and lungs. We outline future research efforts to identify new diagnostic criteria or reproducible early markers of severe disease, to allow for the development of earlier interventions or even pre-emptive treatments.

Summary of recommendations:

1. Earlier clinical recognition of cGVHD requires greater involvement of non-transplant providers and as well as patients/caregivers and can be facilitated by technology such as telehealth (remote physician/patient assessment), teleconferences (remote multidisciplinary conferences) and electronic applications/reporting tools.
2. Early signs and symptoms of cGVHD that are associated with later progression to highly morbid forms of cGVHD need to be identified. This requires careful and repetitive assessments starting prior to transplantation and continuing through formal diagnosis and disease trajectory.
3. Research into prognostic markers in blood, tissue, fluid, imaging and functional testing is needed to identify actionable test results for potential pre-emptive therapy.

Methods: Each working group was created to encourage global engagement in the topic. Groups worked individually to review the relevant literature and create the initial draft of the paper, which was reviewed and commented on by the Steering Committee. Two iterative rounds of comments from the Steering Committee were collected prior to the November 2020 Consensus Conference with appropriate manuscript revisions. Based on additional comments from Conference participants and a 30 day public comment period, the paper was further revised for submission.

Improving Clinical Implementation of the 2014 NIH Consensus Criteria:

Timely recognition of cGVHD could potentially be improved by (1) better education of healthcare providers on the diagnostic criteria for cGVHD, potentially supported by the use of e-Tools (2) delineation of essential cGVHD documentation needed in clinical practice, and (3) by empowering patients to participate actively in symptom monitoring.

1. **Education of healthcare providers including transplant providers, oncologists and primary care providers caring for post-transplant patients: Potential advancements with eHealth**

Healthcare providers may have difficulty recognizing very early signs and symptoms of cGVHD since we know that the application of the current NIH criteria to diagnose cGVHD can be challenging.[20–23] However, knowledge and confidence can be improved by targeted training sessions[24] and several online training platforms are available, though several encompass topics beyond cGVHD diagnosis and development of shorter more targeted training would be helpful (Supplementary Table 1). Similarly, e-Tools can be used to educate and facilitate the implementation of the NIH criteria in clinical practice. Recently, the eGVHD app (www.uzleuven.be/egvhd) was shown to improve the accuracy of GVHD assessment among healthcare professionals.[20,22,23] The app has received CE Marking Type I approval indicating it complies with protection standards, and it has been used by providers worldwide, with USA, China, France, UK and Brazil being the top downloaders. The use of such e-Tools allows clinicians to access the GVHD criteria at the bedside, encourages systematic evaluation of patients, and decreases the diagnosis and scoring errors. Ideally such tools would be integrated

in the electronic health record, although this requires a number of functionalities that could prove very costly (need of user-identification mechanisms, data-protection, interaction and compatibility with other software, medical device regulation compliance and availability of maintenance systems). Integration will therefore require partnership with funding agencies or the private sector. Epic, one of the largest electronic medical record systems, has developed specialized flowsheets to document both acute and chronic GVHD data. Approximately 100 transplant centers are using Epic, with around 40% routinely using the flowsheets. While important and useful to educate the community about the NIH diagnostic criteria, it is important to note that these criteria were meant for cGVHD clinical trials and some patients who do not meet NIH criteria may still have cGVHD that requires treatment.

Teleconferences may also help support and educate community providers who have less experience with cGVHD by facilitating consultation with experts. The COVID-19 pandemic has resulted in the development of more teleconferencing platforms, including many with appropriate security measures to allow HIPAA compliance. The ability to show pictures of physical findings and ask experts questions about new signs and symptoms could facilitate accurate diagnosis of remote patients while also educating local providers about cGVHD.

2. Essential cGVHD evaluations needed in clinical practice

Early recognition of cGVHD offers an opportunity to prevent evolution to more severe disease with irreversible damage.[25] The 2014 NIH recommendations for clinical trials advocate use of a form that captures diagnostic signs and organ severity scoring.[17] Such evaluations

were developed for the setting of clinical trials and likely lack the granularity required to adjust treatments for individual patients. However, completion of the form does ensure that the main organs involved with cGVHD are assessed at each visit. The form is brief and available online at [will add link]. One recommended modification to the 2014 form is the addition of a checkbox for "Abnormality thought to represent cGVHD plus other causes (specify)_____," since organ dysfunction can have multiple contributing causes.

In addition, it is crucial to properly document the baseline status of a patient to correctly identify new abnormalities developing after HCT. With the input of disease/organ experts, we propose the use of a checklist to be completed before HCT to document the presence of signs and symptoms (e.g., dry eyes, restrictions to joint range of motion, lung function tests etc.) that could be subsequently confused with cGVHD if not identified as preceding HCT (Table 1).[26] Post-transplant evaluation for possible cGVHD is standard of care in many centers starting around 100 days after HCT, recognizing that in some patients the diagnosis can be made earlier. Thereafter, clinical follow up of patients is required at least every 1 to 3 months to look for signs and symptoms of active cGVHD until the patient has discontinued immunosuppressive therapy for at least 6 months.[27,28] If abnormalities are detected, prompt referral to a specialized transplantation team for a full cGVHD evaluation and therapy should be considered if the primary provider is uncomfortable with diagnosing and managing cGVHD (Table 2).

3. Active patient involvement in monitoring symptoms

Empowering patients to actively participate in monitoring and reporting their symptoms can facilitate early diagnosis and help monitor treatment response with the potential for improved

outcomes. In several other settings, frequent patient symptom reporting was shown to be effective in improving survival[29] and lowering readmission rates.[30] For cGVHD and other post-HCT complications, tools are being developed to promote recognition of alarm symptoms and help guide appropriate patient response.[31–37] For now, patients should be encouraged to use available information platforms (supplementary table 2)[38], with particular attention paid to reminding patients about the signs and symptoms of cGVHD around D100 or when patients are discharged back to their referring physicians, and away from the transplant center. Future studies should evaluate the value of self-monitoring in the post-HCT setting.

Telemedicine also represents an attractive option for patients who have difficulty accessing cGVHD monitoring by their providers due to distance from the transplant center, limited resources, inconvenience, or restrictions on travel, such as in the COVID-19 pandemic.[39–41] It is important to recognize that the pandemic allowed very rapid advancement of telehealth capabilities, but issues that will need to be considered moving forward are the requirement for medical licensure in the state where the patient resides, coordination of obtaining e-consent prior to the visit, variable coverage based on patient insurance and ability to collect co-pays for services rendered, and lack of access for some patients who don't have electronic devices or internet. In addition, proper evaluation for cGVHD is incomplete without a physical exam.

Earlier recognition of cGVHD before meeting NIH diagnostic criteria :

Greater integration of the 2014 NIH diagnostic criteria into routine clinical practice as described above may allow for more prompt recognition of cGVHD and effective interventions.

However, there are still limitiations to our current diagnostic strategies and even with early diagnosis per the 2014 criteria, outcomes might not be improved. Patients meeting current NIH diagnostic criteria have low rates of responding to initial therapy, as demonstrated in a clinical that enrolled patients within 3 months of cGVHD diagnosis. In this study, 91% of patients had moderate to severe cGVHD and less than 20% were able to be successfully treated, defined as complete or partial response without additional systemic therapy at 1 year.[42] Therefore, identification of early systemic and/or organ specific features that are highly correlated with later development of moderate to severe disease should be a goal for the next 5 years. Successful identification of these features may offer an opportunity to explore the efficacy of very early or even pre-emptive therapy. If new technology proves useful for early diagnosis, it needs to be highly portable, not cost-prohibitive (unless enormous value is demonstated), easily standardized across multiple centers, have high test-retest, intra- and interobserver reliability, require minimal training for operation, and provide easily interpretable data.

<u>Research Goals for non-organ specific early cGVHD identification:</u>

1. Development of prospective observational studies that monitor patients closely for the earliest changes associated with subsequent development of cGVHD are needed. Studies should enroll patients at time of transplant or shortly after and follow them closely in order to detect early signs of disease prior to meeting current diagnostic criteria. Patients will need to be followed for at least 1-2 years post-transplant in order to best correlate early findings with important late outcomes (Figure). There are at least two current trials attempting to identify diagnostic and prognostic signs of cGVHD

including both clinical characteristics and biomarkers, one in pediatric and one in adult patients (NCT04372524, NCT04188912). More specifically, future research efforts could attempt to:

a. Validate that patient reported symptoms can pre-date development of current diagnostic criteria and determine if some of these symptoms are closely associated with later development of moderate or severe cGVHD. Assessment tools that capture common complaints such as pruritus, muscle cramps, etc., such as the Lee Chronic GVHD Symptom scale, already exists and would be easy to study. It is also possible that there are additional common symptoms not currently captured that should be explored as well. Deploying these tools via telemedicine, diaries, and/or electronically (e.g. portable watches) should be studied to better enable future dissemination to patients not actively being seen at a transplant center on a regular basis.
b. Describe the natural history of cGVHD, including diagnostic, distinctive, other or unclassified and common features as previously published in the 2014 NIH-CC on Diagnosis and Staging to understand their true prevalence and prognostic value.[17] These studies could also better document and follow very rare manifestations such as serositis, nephrotic syndrome, polymyositis and peripheral neuropathy and provide a framework to study hypothesized target tissues such as the central nervous system and the endothelium.
c. Collection of clinically characterized blood and tissue samples for both discovery and validation of predictive, prognostic and diagnostic biomarkers

2. Application of machine learning (ML) to help identify risk factors or features highly associated with the development of cGVHD requiring systemic treatment. ML techniques have the advantage of potentially identifying previously unknown associations that do not rely on *a priori* hypotheses based on currently known risk factors or patterns of disease. This approach has been applied to better identify survival patterns in patients with cGVHD based on multiple factors including individual organ involvement and severity.[43] Future efforts using ML should focus on combining known risk factors, provisional early signs and symptoms of disease, biomarkers and other data hypothesized to be associated with cGVHD or its outcome (for example laboratory data, infectious history) to help identify patients at highest risk of development of morbidity and mortality (Table 3). A planned Center for International Blood and Marrow Transplant Research (CIBMTR) study will investigate patient, disease, and transplant-specific factors available within the CIBMTR database with predictive machine learning models to develop a prototype clinical decision support tool to help identify patients at high risk for developing acute and cGVHD (GV20-01).

Organ-specific early cGVHD identification:

Another strategy to approach earlier diagnosis of cGVHD focuses on organs associated with high morbidity and/or mortality: Skin/Fascia, Eyes and Lungs. Our working group included disease experts in each of these areas to help develop both screeing recommendations and potential research approaches. These experts have provided a recommended schedule for screening that at times would involve examinations by a subspecialist or specialized testing,

such as pulmonary function tests (PFTs). We recognize that these recommendations might not always be feasible outside of a clinical trial due to insurance coverage or proximity to appropriate providers/facilities. Additionally, these experts have also provided alternative screening recommendations with triggers of when to involve subspecialists (Table 2).

Skin and Fascial Disease:

Skin fibrosis and fasciitis affect up to 20% of cGVHD patients and are associated with high morbidity, disability, and prolonged immunosuppression.[44,45] There is great need for new assessment techniques including imaging and other biomarkers to diagnose prodromal/early sclerotic disease and reliably assess disease activity. Skin biomarkers could also be explored for their potential early diagnostic value for prodromal cGVHD in other organs.[43,46]

Recommended Clinical Assessments:

1. A comprehensive skin evaluation at every clinic visit is essential with special attention to palpation of anatomic sites with propensity for the development of sclerotic features, particularly the lower extremities and sites of repetitive skin friction and injury such as the waistband.[47,48] The measurement of sclerotic skin and fascial disease is challenging, and there are no validated methods for precise quantification; thus, semi-quantitative markers of severity, including skin pliability, adherence to underlying tissue, and joint range of motion are used to describe the extent of sclerosis.
2. Photographic range of motion (P-ROM)[49] has been refined[50] for response assessment of fasciitis, and should be assessed at each clinic visit. Decreased range of motion in patients with cGVHD is usually related to deep sclerosis affecting the fasciae and may

not be detectable by palpation. Arthralgias, arthritis and prior injury can cause anatomic distortion, making the pre-HCT evaluation critical.

Research Goals:

1. Biomarkers for patients at risk for or with early disease
    a. Systemic prognostic biomarkers: At present, there are no skin specific cGVHD biomarkers, but elafin has previously been identified as an acute GVHD skin biomarker.[51] A proteomic analysis of systemic sclerosis (SSc) patients identified elevated levels of CXCL4 compared to other autoimmune diseases, and levels were associated with the presence of skin fibrosis and progression of disease.[52] Therefore, serial and unbiased proteomic analysis of HCT patients prior to the onset of cGVHD skin fibrosis and/or fasciitis may be able to identify similar high risk biomarkers in our patient population.
    b. Tissue Specific: Skin is one of the most accessible organs from which to develop tissue-based cGVHD biomarkers. However, such biomarkers are lacking, and the potential value of skin biopsy prior to clinically apparent disease is not known. Novel immunohistochemistry markers, especially those studied in connective tissue diseases or acute GVHD,[53] and other means of adding specificity should be explored. Despite the skin being readily accessible, multiple biopsies may be too invasive to serve as a source of serial biomarkers. Improvements in tissue microsampling may enable further biomarker discovery with less chance of complications.[54,55] Additionally, noninvasive microscopic imaging technologies

should be explored further, including bedside confocal microscopy[56] and photoacoustic microscopy.[57]

2. Validation of early signs of disease:
    a. Symptoms: Prodromal features suggestive of evolving cGVHD fibrosis include muscle cramping, edema,[58] new subcutaneous pain and eosinophilia.[44,59] These signs and symptoms should be assessed serially and prospectively to determine sensitivity and specificity for future development of sclerotic disease.
    b. Diagnostic Assessment: Early detection of subclinical sclerotic cGVHD remains an urgent need, and technologies such as MRI,[60] variants of ultrasound,[61] and the Myoton™ device[62] are being studied.
    c. Patient engagement: Self-assessment at regular intervals outside of clinic visits using the photographic range of motion scale (P-ROM) could be assessed and recorded in a logbook or app. The P-ROM has previously been reported as a sensitive marker of disease progression,[49] but its utility in early diagnosis is unknown, especially since joint limitation is a late sign. Similarly, app-based patient-reported symptom assessment (e.g. leg swelling, loss of flexibility, skin tightness) could provide information that triggers prompt evaluation for new onset fibrosis.

Ocular Disease:

Ocular cGVHD can have a severe adverse impact on quality of life.[63,64] Therefore, early diagnosis and targeted therapy for ocular cGVHD could have significant clinical benefits. Ocular cGVHD should not be viewed as a severe form of dry-eye disease, but rather as a rapidly progressive

immune-mediated inflammatory and destructive process of the eye. Current diagnostic criteria, which requires an exam by an eye care provider, are not designed to detect preclinical ocular cGVHD. One clinical trial demonstrated that patients had detectable exam changes as early as 14-28 days post-HCT that were associated with an increased risk of later ocular cGVHD but these changes were not associated with patient reported ocular symptoms at the time of assessment.[65] These findings suggest that evaluation by an ophthalmologist may be required to detect early signs of ocular cGVHD in the preclinical window of opportunity, regardless of patient reported symptoms.

Recommended Clinical Assessments:

1. Comprehensive eye examination conducted by an eye care provider within a month prior to HCT or within 3 months afterwards is necessary to identify aberrations in normal tissue function.[66] (Table 4) During the same visit, patients should be educated about the incidence and potential serious sequelae of ocular GVHD and the warning signs such as dryness, light sensitivity, excessive tearing, foreign body sensation, pain, redness, swelling, mucoid aggregates or change in vision.
2. Follow-up eye examination should be performed at the onset of any eye symptoms or at regular intervals post-HCT. In case of concerning signs or symptoms, prompt referral to a specialist with experience in ocular GVHD is encouraged to confirm the diagnosis and begin treatment.

Research Goals:

1. Biomarkers for at risk/early disease

a. Tissue specific: Validated biomarkers for imminent ocular GVHD are needed using tears or impression cytology. Tear fluid osmolarity change does not differentiate ocular GVHD from other ocular surface diseases.[67,68] However, Interleukin (IL)-6, IL-8, lactoferrin and other neutrophilic biomarkers have shown potential for differentiation.[69–71] EGFR, IL-1Ra, and Fractalkine measured at time of HCT are associated with future development of ocular GVHD.[72,73] Non-invasive imaging such as optical coherence tomography[74] or confocal microscopy[75–78] are also being studied.

2. Validation of early clinical signs of disease

   a. Symptoms: An ocular GVHD-specific and validated questionnaire for early symptoms (e.g. modified OSDI,[79] CDES-Q,[80] etc.) should be developed. Current instruments emphasize late symptoms. In patients with established cGVHD, the patient reported version of the NIH eye score and the 3 eye specific questions of the Lee cGVHD Symptom Scale were both strongly correlated with eye involvement[81], but whether earlier utilization of the PROs would result in earlier referral to ophthalmology and result in early diagnosis is not known, but should be studied.

   b. Serial Exams: Early signs of ocular chronic GVHD may include changes in the eyelid margin, new conjunctival subepithelial fibrosis, if present under the upper or lower palpebral conjunctiva, and hypervascularity and punctate staining of superior bulbar conjunctiva and punctate staining of the superior cornea. The timing of these findings and their association with ocular cGVHD should be

studied by means of frequent evaluations by an ophthalmologist in natural history studies.

Pulmonary Disease:

The 2014 NIH cGVHD diagnostic criteria emphasize new onset of airflow obstruction on pulmonary function testing (PFT), in addition to supportive clinical and radiographic features to diagnose bronchiolitis obliterans syndrome (BOS), the diagnostic manifestation of pulmonary cGVHD.[17] When BOS criteria are strictly applied, most patients already have symptoms and irreversible lung disease, missing an opportunity to recognize earlier signs and symptoms of the disease that may allow earlier and more effective interventions. A randomized double-blind study of patients with newly diagnosed BOS (respiratory symptoms for < 6 months), found that patients receiving inhaled budesonide/formoterol had a statistically significant increase in FEV1 after one month of therapy, and the improvement was maintained after 6 months of therapy,[82] supporting the concept that earlier recognition of disease and intervention may improve outcomes.

Earlier recognition of BOS will require routine screening of asymptomatic patients to detect early declines in lung function. At present, clinical workup for BOS is often initiated based on symptoms; by then, forced expiratory volume in 1 second (FEV_1) may be 30-50% predicted at diagnosis.[83,84] The threshold of FEV_1 <75% predicted as a criterion for significant airflow decline misleadingly implies that BOS is a binary condition present only when lung function is clearly below normal limits. The requirement for an FEV_1/FVC ratio less than 0.70 could also result in missed diagnoses since in BOS, FVC may decline concomitant with FEV_1 due

to impaired exhalation from airflow obstruction. This results in an FEV_1/FVC ratio greater than 0.7, which implies a restrictive process.[85–87]. The 2014 BOS criteria provide other diagnostic challenges. The diagnostic requirement for "absence of infection in the respiratory tract" does not account for the clear association between respiratory viral infections and cGVHD of the lung, [88–91] and can falsely reassure clinicians that declines in lung function are solely linked to the infectious event and reversible. Newer molecular methods of testing for viruses may detect nucleic acid remnants for months after initial infection, further preventing the application of current NIH defined criteria. In addition, spirometric based criteria can not be used for young children given the inherent difficulties performing PFTs in children less than 6-8 years of age.

Recommended Clinical Assessments:

1. Routine serial PFTs or limited spirometry monitoring for all HCT recipients (even asymptomatic) should be performed pre-transplant and then at D100 and one year. For patients with newly diagnosed cGVHD, it is recommended that spirometry be obtained every 3-months.[26]
2. Patients with documented respiratory viral infections (RVI) and concomitant FEV_1 decline should be considered high risk for BOS and followed with short interval PFTs (or spirometry).
3. In interpreting PFT changes, emphasis should be on the relative decline in FEV_1 (e.g. 10% or greater decline in absolute FEV_1) compared to a prior study or the patient's pre-transplant baseline value, rather than a specific threshold (e.g. <75%) compared to normative values.

Research Directions:

1. Identification and validation of biomarkers
    a. Systemic: Aberrant populations of B-cell precursors and dysregulation of B cell homeostasis have been seen in BOS.[92] Potential cytokine and cellular injury makers such as endothelial markers, extra-cellular matrix proteins and lung surfactant / lung proteins have all been reported.[93–96] Replication and validation studies should be performed.
    b. Tissue specific: Novel radiologic techniques, including parametric response mapping (PRM) and hyperpolarized xenon-129 magnetic resonance imaging(MRI) should be tested for their ability to distinguish BOS from other pulmonary conditions.[97–99]
2. Validation of early clinical signs of disease
    a. Diagnostic Assessments:
        1) Define a "pre-BOS" stage, which represents early presymptomatic airflow obstruction. For example, in lung transplantation, BOS-0p is defined as an absolute decline in FEV_1 *or* a decline in forced expiratory volume between 25-75% maximum ($FEF_{25-75\%}$) from baseline (average of the two highest FEV_1 measurements after lung transplantation was defined as the baseline) over consecutive PFTs.[100,101] In HCT recipients, application of similar spirometric criteria for early BOS has been shown to be sensitive for the prediction of BOS (85%) with a high negative predictive value (98%), though a suboptimal positive predictive value (29%).[102] $FEF_{25-75\%}$ measures airflow in distal small airways and has known utility as an early marker of airflow obstruction following lung

transplantation.[103–105] Pre-transplant and early posttransplant declines in $FEF_{25-75\%}$ are strongly associated with the development of BOS after HCT, providing additive value to the diagnostic capabilities of the FEV_1.[106,107]

2) The natural history of BOS after HCT needs to be defined and a routine monitoring strategy is more likely to capture patients in an early disease phase rather than a symptom-based testing approach.[108] Yet, frequent monitoring may be physically and economically challenging, particularly for children and patients living far from a PFT laboratory. Home spirometry with portable handheld devices is feasible in HCT recipients and can be coupled with Cloud-based telemonitoring solutions[109,110] to solve the practical concern of frequent spirometric monitoring of high risk individuals.[111]
3) Clarify the role of respiratory infections in the development of BOS and update the BOS diagnostic criteria, if appropriate. Several studies have shown an increased risk of pulmonary impairment following respiratory viral infections and an associated increased risk of NRM.[88,89,91] Currently, the diagnosis of BOS requires exclusion of respiratory pathogens, but cGVHD patients often have persistent viral shedding or frequent recurrent infections. Therefore, some modification to the diagnostic criteria regarding persistent decline in FEV_1 despite persistence of a respiratory pathogen to allow for the diagnosis of BOS, should be explored.
4) Alternatives to PFTs in children are needed. Non-invasive pulmonary testing that is safe, feasible, and reproducible in children, such as the nitrogen multiple

breath washout test (which measures ventilation inhomogeneity as a measure of airway obstruction) have been successfully applied to infants with cystic fibrosis,[112] children with early airway pathology following lung transplant,[113] and have been shown to be highly sensitive for detecting early lung cGVHD in adults after HCT.[114]

Conclusions

Redefining how we recognize cGVHD earlier in its natural history will be a major undertaking, but has the potential to positively impact our patients given the limitations of our current diagnostic criteria, particularly the concern of irreversible organ damage prior to meeting the current criteria. If earlier diagnostic signs and symptoms can be validated, this will allow for the development of pre-emptive interventions with the hope of preventing much of the morbidity and mortality that patients with moderate to severe cGVHD currently face. Discovery and validation of early features of cGVHD will involve patients/caregivers, transplant providers and our subspecialty colleagues. Natural history trials need to enroll patients before cGVHD has developed. These trials should include serial sample collections for biomarker assessments, patient involvement (to assess both symptom burden as well as interventions such as handheld spirometry) and standardized documentation of physical exam findings. These studies should begin in the next 3 years because they will take years to yield definitive data. Machine learning projects are already underway with data currently available in the CIBMTR to develop tools to better predict future development of cGVHD, which can be further refined by incorporating data from these natural history studies. Diagnosis of ocular and

genital involvement is a particular challenge because current diagnostic criteria require assessment by a subspecialist. Engagement with these subspecialists will be essential to help develop early assessment tools (likely patient symptom measures) to help prompt early referral. In the next 3-7 years, the ability to recognize pre-clinical cGVHD will allow studies of agents targeted to underlying pathophysiology and delivered preemptively.

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versus-

Host+Disease+on+Quality+of+Life&stitle=Biol.+Blood+Marrow+Transplant.&title=Biology+of+Blood+and+Marrow+Transplantation&volume=21&issue=9&spage=1687&epage=1691&aulast=Sun&aufirst=Yi-Chen&auinit=Y.-C.&aufull=Sun+Y.-C.&coden=BBMTF&isbn=&pages=1687-1691&date=2015&auinit1=Y&auinitm=-C.

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Figure: Design of studies to improve early chronic GVHD diagnosis

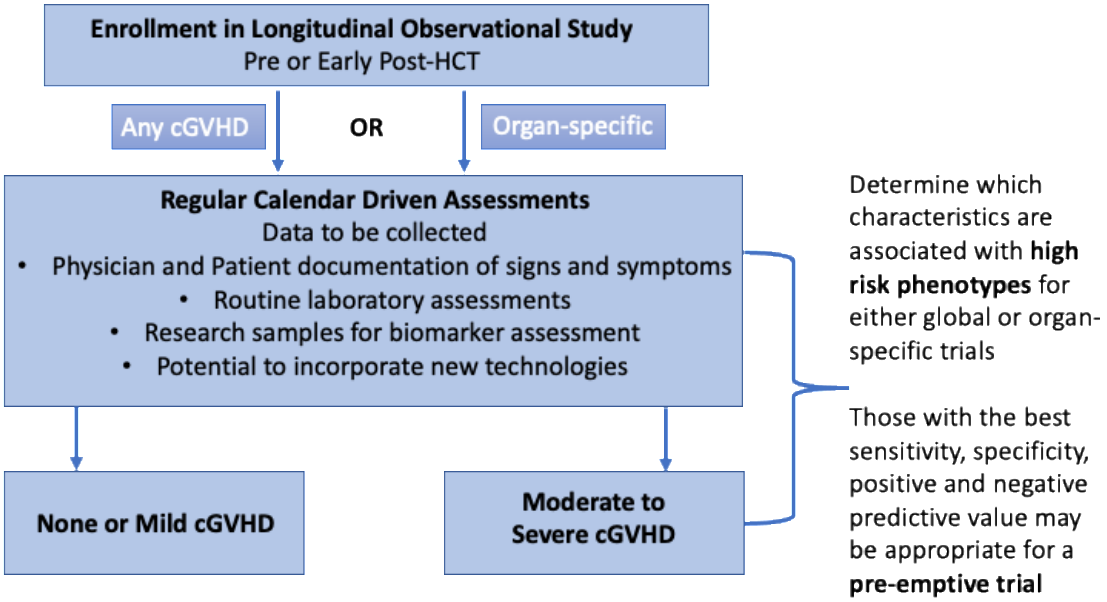

Table 1: Baseline evaluation to be done before transplantation and Day +100 post-transplantation adapted from[17,26]

Organ System	Required items
Skin (including nails and hair)	Document baseline skin abnormalities (scars, vitiligo, etc) with photo-documentation, if possible.
Mouth	Document linea alba, lichenoid changes, mucosal abnormalities and restriction of mouth opening.
Eye	Document dry eyes and other eye symptoms, use of prescribed or over-the-counter eye drops
Lung	Pulmonary function tests including: spirometry (FEV_1, FVC, FEV_1/FVC ratio, $FEF_{25-75\%}$), lung volumes (VC, TLC, RV), and DLCO.^
Liver	Bilirubin, AST, ALT, Alk phosphatase
GI tract	Document anorexia, nausea, vomiting, diarrhea, dysphagia, food allergies/intolerance etc.
Fascia/joints	Document any limb mobility issues and photographic range of motion (P-ROM)[50] NB: For the pediatric adaption of P-ROM see EBMT handbook/cGVHD[115]
Genital	Document any evidence of lichenoid lesions, erythema, ulcers, fibrosis or phimosis in males (ideally women will be evaluated by a gynecologist)

^PFTs may not be feasible in patients <7 years of age.

Table 2: Follow-up evaluation starting from 100 days (D100) post-HCT adapted from[17,26]

Organ System	Required items	Threshold for referral to specialized transplant team
Skin (including nails and hair)	Conduct a complete skin, nails and hair evaluation. The patient should be asked whether any change in appearance has been noticed.	New onset of lesions suggestive for cGVHD per 2014 NIH-CC guidelines
Mouth	Evaluate for any lichenoid changes, ulcers, erythema and restriction of mouth opening. The patient should be asked whether any pain, difficulty swallowing or dryness is perceived.	New onset of lesions suggestive for cGVHD per 2014 NIH-CC guidelines
Eye	Ask about any ocular symptoms (dryness, excessive tearing, foreign body sensation, redness, difficulties opening eyelids, photophobia, etc.). Ophthalmology evaluations are recommended at least yearly after HCT.	Symptoms suspicious for onset of ocular GVHD and change from pre-HCT or previous post-HCT examination
Lung	Obtain pulmonary function tests including: spirometry, lung volumes and DLCO at D100, 1 year, and yearly. Spirometry is recommended every 3 months in patients with cGVHD. Lung volumes and DLCO can be performed more frequently if clinically indicated.	Decline in the FEV1 of 10% or greater from the patient's baseline or D100 assessment • Recommend short interval repeat testing (within 2-4 weeks) or a referral to a cGVHD center for workup of early BOS
Liver	Obtain bilirubin, AST, ALT, Alk phosphatase	Rise of bilirubin or liver enzymes above 2014 NIH-CC thresholds
GI tract	Assess for nausea, anorexia, dysphagia, diarrhea or weight-loss.	New onset of signs/symptoms suggestive for cGVHD per 2014 NIH-CC guidelines

Fascia/joint	Conduct functional and P-ROM assessment NB: For the pediatric adaption of P-ROM see EBMT handbook/cGVHD[115]	In clinical trials, a 2-point difference in total P-ROM is considered clinically relevant[50], but if normal pre-HCT, any change from baseline may be significant
Genital	Evaluate for any evidence of lichenoid lesions, erythema, ulcers, fibrosis or phimosis in males (ideally women would be evaluated by a gynecologist). Ask about any change in appearance, pain or dryness.	New onset of signs/symptoms suggestive for cGVHD per 2014 NIH-CC guidelines
Blood count	WBC with differential	Rising eosinophilia

Table 3: Potential factors to be assessed in clinical studies for discovery and validation of early chronic GVHD markers

Factor	Considerations
Clinical characteristics	Known risk factors (ex. PBSC, aGVHD) Other demographic/clinical information
Signs/Symptoms	Provider-assessed signs/symptoms • All signs/symptoms of cGVHD per the 2014 Diagnosis and Staging NIH-CC • Subspecialty engagement for certain organ specific assessments (ex. ophthalmology, dermatology) Patient engagement/PRO • Lee cGVHD Symptom Scale • Home monitoring of P-ROM • Hand held spirometry • Ocular Surface Disease Index
Biologic	Routine lab monitoring (ex. eosinophils) Cellular and protein biomarkers Additional -omics (ex. epigenetics, transcriptomics)
Technology	Lungs – parametric response mapping, hyperpolarized xenon-129 MRI Skin – optical coherence tomography (non-invasive “biopsy”), myoton (stiffness and elasticity measurement)

Table 4: Recommended best practice and optional components of ophthalmology assessments.

	Examination pre- and post-HCT
Best Practice components	Best corrected visual acuity
	Intraocular pressure
	Schirmer's test without anesthesia
	Tear-film breakup time
	Slit lamp examination including: - Lid/blepharitis assessment - Ocular surface staining - Conjunctival redness and fibrosis - Lens
	Assessment of Meibomian gland function: Quality and quantity of meibum
	Symptom questionnaire
Optional components	- Meibography - Corneal esthesiometry - Confocal microscopy - Photographic documentation of lids, tarsal and bulbar conjunctiva, cornea, fundus, - InflammaDry® - Impression cytology - Specular microscopy

Supplementary Table 1: Health care provider education resources and diagnostic applications

Training videos	• For nurses: https://www.professionalabstracts.com/ebmt2018/iplanner/#/presentation/25 (limitation - presents information on both diagnosis and treatment; consideration for development of exclusively diagnostic materials
Scientific Societies	• https://gvhd.eu/resources/ • https://www.cibmtr.org/manuals/fim/1/en/topic/f2100-q234-406 • https://www.astct.org/asbmt/professional-development/online-learning/gvhd---assessing-staging-and-following-acutechronic-disease

Supplementary Table 2: Patient education resources and websites

Patient advocacy groups and peer support groups	• https://www.bmtinfonet.org/video/category/graft%20versus%20host%20disease • https://cowdenfoundation.org/gvhd-home/2019-physician-presentations/ • https://www.macmillan.org.uk/cancer-information-and-support/treatment/types-of-treatment/stem-cell-and-bone-marrow-transplants/donor-stem-cell-allogeneic-transplants/graft-versus-host-disease-gvhd#chronic_graft-versus-host_disease
Scientific Societies	• https://gvhd.eu/resources/ • https://bethematch.org/patients-and-families/life-after-transplant/physical-health-and-recovery/graft-versus-host-disease-basics/