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NIH Chronic Graft-Versus-Host Disease Consensus Conference 2025 Update

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In 2020, the third NIH Consensus Development Project on Criteria for Chronic Graft-versus-Host Disease (GVHD) Clinical Trials was held with the goals of identifying gaps in understanding, prevention and treatment of chronic graft-versus-host disease (GVHD) and making actionable recommendations that would advance the field. An interim meeting was held in October 2024 to review progress on the 2020 recommendations. Each group was charged with reviewing their previous recommendations, assessing whether the field is on track to eventually achieve the goals, and considering whether recommendations should be modified in light of new data or insufficient progress. This manuscript summarizes the Working Groups' reports and helps define the research agenda for future studies in chronic GVHD. Overall, modest progress has been made on most initiatives.

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Some studies in progress will address key recommendations and results are eagerly anticipated.

On October 16 to 17, 2024, the 7th International Chronic Graft-versus-Host Disease Symposium took place in Vancouver B.C. As part of the scientific program, the leaders of the four main NIH Consensus Conference working groups (WG) and a fifth task force dedicated to atypical manifestations delivered presentations about the accomplishments in their respective areas since the publication of the 2020 Consensus Recommendations. Groups were asked to score progress on their 2020 recommendations [1–6] as Red (no significant progress), Yellow (some progress), or Green (substantial progress). In areas that were Red or Yellow, groups were asked to determine what would be needed to achieve success for their recommendation, or whether the recommendation should be retired as no longer relevant or achievable. The presentations and discussions are summarized below and an Executive Summary provided in Table 1. Members of each WG are shown in Table 2.

WORKING GROUP I: ETIOLOGY AND PREVENTION

Kirsten Williams, Stefanie Sarantopoulos

Working group I was tasked with developing consensus around clinical trials addressing prevention of moderate to severe chronic GVHD [1]. The 2020 Working Group I recommendations included the need to monitor the risks of reducing moderate to severe chronic GVHD, most notably, the potential to incur higher rates of relapse and delayed or impaired immune reconstitution. Since publication of these original WG recommendations, randomized trials of post-transplant cyclophosphamide (PTCy) show impressive prevention of chronic GVHD in the context of reduced intensity conditioning (RIC). New studies are evaluating lower doses of PTCy to maintain chronic GVHD prevention while decreasing toxicities, or combining PTCy with other agents to further reduce GVHD.

Conduct trials to prevent moderate to severe chronic GVHD, which is associated with excess long-term morbidity and mortality (green)

PTCy has emerged as the most studied and now most widely accepted approach. Two large prospective randomized trials have been published. In the largest study, only 7% of those who received PTCy along with tacrolimus and mycophenolate mofetil (MMF) developed moderate to severe chronic GVHD by one year, compared to 17% with standard tacrolimus-methotrexate prophylaxis [7]. Similarly, in those who received PTCy with cyclosporine the 2-year event rate of extensive chronic GVHD was 16% compared to 48% with cyclosporine/MMF without PTCy [8]. Notably, these studies included older recipients who received reduced intensity conditioning regimens and largely human leukocyte antigen (HLA)-matched donors. Another large, prospective, multi-institutional, randomized trial using PTCy after myeloablative hematopoietic cell transplantation (HCT) did not reduce extensive chronic GVHD two years after HCT compared to tacrolimus and methotrexate [9] but the PTCy arm lacked additional calcineurin inhibitor which is now standard of care.

There are two other emerging strategies to prevent chronic GVHD, the ORCA-T platform and the addition of ruxolitinib to calcineurin inhibitor and methotrexate. The ORCA-T platform utilizes staged infusions of hematopoietic stem cells with purified regulatory T cells, followed by conventional T cells with or without tacrolimus prophylaxis [10]. In a single arm study, chronic GVHD was reduced compared to historical control studies with only 1/12 patients developing mild chronic GVHD, none with moderate to severe, and a preserved one year relapse free survival of 75% [11]. A large randomized multicenter trial of ORCA-T versus tacrolimus and methotrexate showing better chronic GVHD-free survival with ORCA-T was reported in an abstract at the 2025 European Bone Marrow Transplant meeting. In a single arm study, addition of ruxolitinib after HCT (~day 45) to tacrolimus and methotrexate prophylaxis using a reduced intensity regimen led to low rates (16%) of moderate to severe chronic GVHD at 2 years [12]. Based on these data, a large randomized cooperative group trial (BMT CTN 2203) has just opened. Although these data are limited by patient numbers and short follow-up, they are encouraging in terms of mitigating the risk of chronic GVHD without increasing the risk of relapse.

Table 1
Summary of Progress on 2020 Recommendations

WG	2020 Recommendation	Progress	Comments on Progress and Next Steps
1.1	Conduct trials to prevent moderate to severe chronic GVHD, which is associated with excess long-term morbidity and mortality	Green	• Large prospective trials have evaluated PTCy, CD34 selection, and ATG. • Ex-vivo T cell manipulation strategies should be tested in randomized trials • Longer-term follow-up is needed
1.2	Evaluate T-cell depletion strategies, with attention to potential impairment of immune reconstitution and antitumor effects	Yellow	• Immune reconstitution studies are very limited. • Clinical studies need longer-term follow-up to monitor for potential late relapses and immune impairment
1.3	Evaluate graft engineering strategies, modified schedules for weaning immunosuppression, protection of primary and secondary lymphoid organs, and maintaining a balance between immune effector cells and immune regulatory cells.	Yellow	• Early trials of novel lymphoid sparing regimens, graft engineering are ongoing • Data are insufficient to support standardized strategies for immune suppressant tapering, and lack of progress indicates they may not be feasible • More data are needed to understand the role of the host tissue microenvironment
1.4	Test risk mitigation strategies for secondary insults, such as infection prevention.	Red	• One study is testing mitigating infectious risks • Lack of progress suggests these studies may not be feasible.
1.5	Conduct high throughput "multiomics" studies to identify novel targets	Red	• Large data sets exist but do not include sufficient patients receiving the new GVHD prophylaxis regimens • Studies that address molecular mechanisms are needed
2a.1	Facilitate earlier clinical recognition of chronic GVHD through greater involvement of all HCT stakeholders	Yellow	• Educational supplements are available • An eGVHD App is available • Chronic GVHD scoring available in some but not all electronic medical records • Telehealth ability largely lost due to federal regulations • Studies examining dissemination and impact are required
2a.2	Identify early signs, symptoms, and other diagnostic determinants that are reliably associated with chronic GVHD and later progression to highly morbid forms of chronic GVHD	Yellow	• Several large studies ongoing to correlate clinical and biologic phenotypes to chronic GVHD development • Application of artificial intelligence should be studied
2a.3	Incorporate study of prognostic markers in blood, tissue, fluid, imaging, and functional testing to identify actionable early indicators for potential pre-emptive therapy.	Yellow	• Studies seeking organ-specific markers for early identification of chronic GVHD are underway • New technology assessments of tissue samples are needed • No evidence that early intervention is associated with improved outcomes yet. Adoption should await study results
2b.1	Identify risk assignment biomarkers	Yellow	• New published data available, but ongoing need for robust biomarkers with adequate test characteristics for preemptive therapy application
2b.2	Conduct preemptive therapy trials	Yellow	• First dedicated chronic GVHD preemptive therapy trial testing belumosudil vs. placebo has launched • Design future trials with risk assignment biomarker-based eligibility
3.1	Incorporate correlative studies into clinical trials	Red	• Published correlative analyses from large, industry-sponsored trials are lacking to date • Single or small multicenter trials are typically underpowered and/or underfunded to conduct meaningful biological correlatives • Strong collaboration between academia, industry and patient advocates is needed • Encourage industry to include correlative studies into new trials of chronic GVHD • Form international academic collaborations to perform well-designed clinical trials with a biology-based approach

(*continued*)

Table 1 (*Continued*)

WG	2020 Recommendation	Progress	Comments on Progress and Next Steps
3.2	Design steroid-free monotherapy trials for initial treatment of chronic GVHD	Yellow	• Studies to move systemic agents into first-line settings are ongoing • To maximize knowledge gained from the available population, platform trials, master protocols, use of common control groups for comparison with novel agents or digital twins for control populations is highly recommended
3.3	Limit heterogeneity in clinical trials for treatment beyond first-line	Yellow	• Organ-specific responses to therapeutic agents are largely inferred from secondary analyses of larger trial data sets • Recent prospective trials are targeting more specific phenotypes
4.1	Phenotype highly morbid forms of chronic GVHD clinically and biologically	Yellow	• Knowledge is currently based mainly on cross-sectional analyses • Prospective trials are starting
4.2	Use novel trial designs for small populations	Red	• Novel trial designs have not been used for chronic GVHD trials • Explore the use of umbrella and basket trials, and trials based on Bayesian approaches • Combination trials may be either performed with randomized controls or with a step-up design
4.3	Test new approaches for early identification and treatment of highly morbid forms	Yellow	• Task force for early identification of lung chronic GVHD formed • The natural history CATCH trial has finished enrollment and is awaiting sufficient follow-up • Opportunity to analyze inciting events like desiccation stress for ocular chronic GVHD and infections for lung chronic GVHD, including potential early interventions
4.4	Establish primary endpoints for clinical trials addressing highly morbid manifestations	Red	• Task force for skin sclerosis has proposed phenotype-specific response criteria • Include alternative endpoints in prospective clinical trials and observational trials as secondary endpoints to establish their value predicting functional and long-term success
A.1	Increase awareness of atypical chronic GVHD in the literature and with clinicians, with proposed case definitions and discussion around challenges with diagnosis of atypical chronic GVHD.	Yellow	• Continued education of front-line cellular therapy and noncellular therapy health care (physicians, physician assistants, nurse practitioners, nurses, pharmacists) • Integration of atypical chronic GVHD into future NIH diagnostic criteria
A.2	Increase understanding of the incidence, morbidity and mortality from atypical chronic GVHD.	Yellow	• Increasing number of publications • Need to capture atypical chronic GVHD manifestations in prospective, observational natural history studies of chronic GVHD (not currently done) and in future chronic GVHD therapeutic clinical trials.
A.3	Increase understanding of the pathophysiology of atypical chronic GVHD	Yellow	• Increased understanding of biologic underpinnings of central nervous system and renal GVHD • Need improved understanding of restrictive lung disease, pancreatic, liver, and hematopoietic chronic GVHD, including similarities and differences with other autoimmune diseases. Clinical studies should have biologic correlates. • Development and study of new preclinical models with emphasis on understanding therapeutic interventions.

GVHD indicates graft-versus-host disease; PTCy, post-transplant cyclophosphamide; CD34, cluster determination-34; ATG, antithymocyte globulin; HCT, hematopoietic cell transplantation; A, atypical manifestations.

Evaluate T-cell depletion strategies, with attention to potential impairment of immune reconstitution and antitumor effects (yellow)

T-cell depletion via CD34 selection reduced extensive chronic GVHD two years after myeloablative HCT, albeit with higher nonrelapse mortality, in a large multicenter randomized study [9]. Naïve T cell depletion has also emerged as a promising method to avert severe chronic GVHD, with combined phase II trials nearly abrogating chronic GVHD [13]. A few publications have suggested that reduction of moderate to

severe chronic GVHD may be associated with higher relapse rates with longer follow-up, including one retrospective study with PTCy and another with antithymocyte globulin (ATG) [14,15]. Long term studies have shown that patients who develop moderate to severe chronic GVHD despite these approaches (PTCy and ATG) have less relapse and higher survival [14,16,17]. While most studies of these newer approaches have not shown higher rates of relapse, longer follow-up of prospective randomized studies with large patient numbers will be critical to fully evaluate the relapse risk in the context of newer chronic GVHD prevention strategies.

In terms of immune reconstitution, a recent study from a large prospective trial (BMT CTN 1703) showed reduced T cell diversity following PTCy that persisted for 2 years after HCT as compared to tacrolimus/methotrexate standard prophylaxis [18]. Long term studies are needed to investigate immune reconstitution and tumor surveillance after newer strategies. Some data limited to one year after HCT suggest that PTCy and $\alpha\beta$T-cell and CD19-B cell depletion lead to delayed immune recovery [19,20].

Evaluate graft engineering strategies, modified schedules for weaning immunosuppression, protection of primary and secondary lymphoid organs, and maintaining a balance between immune effector cells and immune regulatory cells (yellow)

Strategies that protect primary and secondary lymphoid organs remain exploratory, such as anti-CD117 and anti-CD47 conditioning regimens [21]. Refined approaches to balance immune activating and regulatory subsets have been studied, including T-cell, B-cell, and natural killer (NK) cell approaches. In one small haploidentical donor study to treat acute myelogenous leukemia, regulatory T cells were adoptively transferred prior to the infusion of conventional T cells and a CD34-selected product, resulting in low rates of severe chronic GVHD and relapse [22]. Another haploidentical CD34-selection approach was similarly promising, whereby naive T cells were depleted before NK cells were infused [23]. A small Phase I study of fostamatinib suggests potential benefit of eliminating only the B cell subset that was aberrantly activated through the B Cell Receptor (BCR) while allowing recovery of a normal B cell compartment to avert chronic GVHD [24]. Novel immunosuppressant taper strategies have not been evaluated.

Test risk mitigation strategies for secondary insults, such as infection prevention (red)

While there has been limited progress on this recommendation, one study suggested letermovir prophylaxis reduced rates of acute and chronic GVHD [25].

Conduct high throughput "multiomics" studies to identify novel targets (red)

One study incorporated multiparameter approaches including RNA sequencing and metabolomics and demonstrates promise for this strategy [26].

Executive summary for WG1: Major progress has been made regarding the efficacy of chronic GVHD prevention strategies early after HCT. Longer follow-up is needed given theoretical concerns about disease relapse rates and immune reconstitution delays that may occur under certain conditions. Further investigation of the factors that affect outcomes will enable improved and more personalized approaches. With the advent of these chronic GVHD prevention strategies, the number of patients available for large clinical trials may be limited, requiring the research community to work together to answer the most critical questions. Given the lower incidence of chronic GVHD, strategies such as protection of secondary lymphoid organs and preventing secondary insults like infections as a means of decreasing chronic GVHD may not be testable or necessary approaches. The field is still searching for biomarkers that can identify patients who might benefit from specific prevention strategies.

WORKING GROUP IIA: CLINICAL IMPLEMENTATION AND EARLY DIAGNOSIS

Corey Cutler, Carrie Kitko

Working Group IIa was tasked with identifying strategies to improve the early identification of chronic GVHD and to increase the use of the NIH consensus criteria for the diagnosis of chronic GVHD in the community [2]. Earlier clinical recognition of chronic GVHD requires greater involvement of all HCT stakeholders, including nontransplant providers as well as patients and caregivers. Recognition of the early signs, symptoms, or other diagnostic determinants of chronic GVHD that are reliably associated with later progression to highly morbid forms of chronic GVHD may allow earlier effective treatment and prevent long term morbidity and mortality.

The earlier identification of chronic GVHD was to be accomplished through 4 specific interventions:

1. Education of transplant and oncology care providers in the community
2. Improved education and engagement of patients and their caregivers in monitoring for symptoms
3. Planned assessment of chronic GVHD target organs at regular intervals, with an accurate documentation of baseline function of certain organs (for example, eyes)
4. Improved utilization of remote monitoring and assessments

Facilitate earlier clinical recognition of chronic GVHD through greater involvement of all HCT stakeholders (yellow)

Several broad educational initiatives have been developed and are being disseminated to community-based providers with a goal of increasing awareness of the signs and symptoms of chronic GVHD. An entire educational journal supplement on the clinical manifestations of chronic GVHD has recently been published [27], and an educational video directed towards patients and their families is nearing completion. The eGVHD app is now embedded into the American Society of Transplant and Cellular Therapy (ASTCT) handheld application to facilitate more accurate chronic GVHD scoring, although it is unclear if this app is used in the community [28,29]. While the handheld application is freely available, integration of chronic GVHD scoring directly into the electronic medical record is not available at most clinical sites.

Several strategies are being used to accurately capture chronic GVHD NIH scoring in the community. While telehealth is largely being phased out with the end of the coronavirus pandemic, a hybrid model of standard physician assessments with electronic health-facilitated integrated care models is being piloted at several European sites and results have been reported in abstracts, with a new module being developed to help patients independently detect chronic GVHD-related symptoms.

Identify early signs, symptoms, and other diagnostic determinants that are reliably associated with chronic GVHD and later progression to highly morbid forms of chronic GVHD (yellow)

Early identification of chronic GVHD-associated changes in vulnerable end-organs using novel techniques and screening strategies is important to prevent progression to highly morbid forms. Several groups of subspecialists are applying novel technology to their respective organs of interest. The goal is to prevent irreversible organ injury through interventions (either local or systemic) which are effective and applied in a timely fashion. While there are several studies examining commonly affected organs, there are few organized efforts around the early identification of the more atypical manifestations of chronic GVHD.

The routine use of PFTs sequentially after HCT and at the time of chronic GVHD diagnosis is an ASTCT guideline [30], but has poor adherence although early detection of airflow obstruction can be useful in the early identification of bronchiolitis obliterans syndrome (BOS) [31,32]. Soluble biomarkers [33] and novel imaging techniques may be useful to predict BOS [34,35]. Simple home spirometry may be an inexpensive way of remotely monitoring pulmonary function and may identify BOS earlier [36].

Routine ophthalmologic evaluation following HCT is also important to detect and treat ocular chronic GVHD before permanent damage occurs. A pre-HCT exam should be obtained as a baseline, as dry eye is a relatively common finding among the general population and those who have received chemotherapy. With regular ophthalmologic screening, a high incidence of ocular chronic GVHD is noted, and some tear biomarkers may be useful in diagnosis [37].

In cutaneous disease, there are efforts underway to use machine learning to help identify skin chronic GVHD [38] and several candidate biomarkers are being prospectively tested to identify early changes associated with sclerosis. Novel measurement technology, such as hyperspectral imaging [39] and the Myoton device [40] are being tested to determine if they can identify sclerosis prior to obvious clinical manifestations.

Some potential limitations to earlier and more frequent monitoring include lack of subspecialty providers with appropriate expertise and potential delayed access due to long wait lists for appointments. While some tests like PFTs can be easily scheduled based on known monitoring intervals (D100, D180, etc.), there could still be potential insurance denial of coverage. Current and future research efforts should focus on identification of specific physical exam findings or home monitoring with a hand-held spirometer that could be incorporated into local screening, and when identified could then prompt referral to the appropriate subspecialist.

Incorporate study of risk assignment markers in blood, tissue, fluid, imaging, and functional testing to identify actionable early indicators for potential preemptive therapy (yellow)

Several ongoing studies attempt to detect the earliest clinical manifestations and predict the onset of chronic GVHD. The CATCH (Close Assessment and Testing for Chronic GVHD) study (NCT04188912) is a prospective, observational study which collects both clinical data and patient samples, with the goal of identifying clinical or biological characteristics associated with the onset of chronic GVHD [41]. Other studies use machine learning algorithms with large clinical datasets or other approaches to try to identify patient phenotypes that predispose to the development of chronic GVHD. However so far these efforts, for example the CIBMTR GV20-01 and GV22-02 studies, have not been successful.

Executive summary for WG IIa: Looking ahead, Working Group IIa recommended the field needs to identify metrics of success for the implementation of community-based efforts in the early identification and accurate diagnosis of chronic GVHD and conduct studies where initial staging of chronic GVHD is compared before and after implementation of educational interventions. Ultimately, studies focused on early intervention to prevent long-term morbidity are required to show that earlier diagnosis of chronic GVHD is beneficial.

WORKING GROUP IIB: PREEMPTIVE THERAPY

Joseph Pidala, Geoffrey Hill

Working Group IIb focused on preemptive therapy of chronic GVHD, a previously untested point of intervention in the traditional schema of chronic GVHD therapeutics [3]. Preemptive therapy was defined as an intervention delivered post-HCT and targeted to those with high risk for chronic GVHD development, thus conceptually distinct from universal prophylaxis delivered broadly or primary therapy at time of full clinical presentation of chronic GVHD. WGIIb focused on two core domains of 1) risk assignment to identify appropriate subjects for a preemptive intervention; and 2) features of ideal preemptive therapeutics. For the first, the WGIIb proposed that risk assessment could include early clinical features not fully meeting NIH Consensus Diagnostic Criteria and/or risk assignment biomarkers associated with subsequent development of chronic GVHD. However, the test characteristics of any given risk assignment model are critical, especially high positive- and negative-predictive values (PPV, NPV), given implications of over- or under-treatment. As of 2025, no risk assignment model is ready for use and only one preemptive trial with eligibility defined clinically is ongoing.

Identify risk assignment biomarkers (yellow)

Given the limitations of existing evidence, a major priority was the identification of risk assignment biomarkers through prospective multi-institutional studies. Moderate progress has been achieved through publication of multicenter data on chronic GVHD risk assignment biomarkers. Additional studies are actively recruiting participants and will have future results. One major published study evaluated risk assignment biomarkers in 982 subjects from two prior BMT CTN trials [42]. Some graft source-specific (bone marrow (BM) versus peripheral blood mobilized stem cells (PBSC)) findings emerged, where MMP3 (+CXCL10) in BM vs. CXCL9 and DKK3 (or MMP3) in PBSC were associated with subsequent chronic GVHD risk. In general, PPV was low (ranged from 22%-35%) and NPV was higher (ranged from 79%-92%). Other day 90 post-HCT biomarkers (ST2, CD163, DKK3) were associated with nonrelapse mortality. Other unpublished data was reviewed from the ABLE (Applying biomarkers to long-term effects of child and adolescent cancer treatment, NCT02067832) study, and large prospective studies with potential to further develop risk assignment biomarkers are anticipated (NCT04372524, NCT04188912). Decreased incidence and prevalence of chronic GVHD due to evolving primary prophylaxis approaches will likely affect biomarker performance and application [43]. WGIIb acknowledged the heterogenous nature of the clinical manifestations and known pathophysiology of chronic GVHD [44], highlighting the potential difficulty in assigning a biomarker that can capture this spectrum in its entirety and predict disease. An alternative approach is to develop dysregulated “immune signatures” that represent known pathways of chronic GVHD and to which targeted therapeutics are available. This has recently been demonstrated for IL-17 and CSF-1 dysregulation such that this approach could be explored prospectively in clinical studies with relevant therapeutics (e.g. belumosudil or axatilimab) [45].

Conduct preemptive therapy trials (yellow)

Moderate progress has been made through industry partnerships and increased interest in early treatment, resulting in at least one preemptive

therapy trial. This study is a randomized, double-blinded, multicenter trial (NCT05996627) for patients with very early chronic GVHD manifestations (although not sub-clinical or based on a risk assignment biomarker) which randomizes subjects to belumosudil vs. placebo with a primary endpoint of need for subsequent systemic immune suppressive therapy. The trial is responsive to the key considerations outlined by WGIIb, especially in utilizing an agent that largely meets the major criteria for ideal preemptive therapy. Additional next-stage preemptive trials with eligibility based on risk assignment biomarkers are needed, but rely upon progress in biomarker development and validation. The evolving therapeutic landscape with four FDA-approved agents in steroid-refractory chronic GVHD suggests other interventions could be tested [46–49].

In the absence of a validated biomarker or immune signature, preemptive studies in chronic GVHD will need to focus on patient groups at high risk based on clinical parameters and use of agents with low potential for toxicity/harm. In this regard, a well-tolerated oral agent like belumosudil would seem attractive.

Executive summary for WGIIb: While there has been progress in identifying risk assignment biomarkers, none has sufficient PPV and NPV yet to guide preemptive trials. Given the heterogeneous nature of chronic GVHD, focusing on identifying subclinical indicators of final common pathways in blood, or focusing on tissue rather than blood, might be most fruitful. Until more progress is made in this area, preemptive trials will necessarily need to be limited to very safe and well tolerated agents. One multicenter preemptive study based on clinical criteria is ongoing and results are awaited.

WORKING GROUP III: TREATMENT

Zachariah DeFilipp, Hildegard Greinix

The focus of Working Group III was to establish priorities for future clinical trials that would advance the field of chronic GVHD therapeutics [4]. Several gaps were identified. First, our understanding of the interactions between clinical manifestations of chronic GVHD and the biological impact of targeted therapies remains preliminary. Therefore, detailed correlative scientific studies should be incorporated into prospective clinical trials to evaluate the biological effects of systemic therapeutics in patients with chronic GVHD and to evaluate how these effects correlate with clinical outcomes. Prioritization of biological correlates in the context of clinical trial designs could ultimately redefine treatment paradigms of chronic GVHD into a more personalized approach, in which a patient's biomarker signature could be used to select therapies. Next, clinical trials should challenge the current standard of care for initial systemic therapy by investigating targeted therapeutics in steroid-free study designs. Finally, clinical trials for treatment-refractory disease should seek to limit heterogeneity within eligibility criteria, by selecting patients with incomplete or suboptimal responses who are early in their disease course or who have common clinical manifestations. Working Group III did not address clinical guidance for the use of the 4 FDA-approved agents, either as single agents or in combination, because comparative data are still very limited.

Incorporate correlative studies into clinical trials (red)

Treatment options for patients with chronic GVHD have expanded considerably in recent years, led by unprecedented large multicenter randomized trials through collaboration with industry [47,48]. Although WGIII recommended that biological samples should be collected and detailed correlative scientific studies should be conducted in the context of clinical trials, recently published industry-sponsored trials leading to FDA approval of novel immunosuppressive agents unfortunately did not include these correlative analyses [47–49].

Single or small multicenter trials are typically underpowered and/or underfunded to conduct meaningful biologic correlatives. Therefore, international collaborations in the academic field as well as with industry should be pursued to perform well-designed clinical trials with a biology-based approach. To understand the associations between clinical manifestations, biomarker profiles, and pathophysiologic inferences and how they change from baseline to the time of response assessment in a clinical trial is not a trivial task. It requires a strong research infrastructure, material storage in a biorepository facilitating a communal effort to perform individual assays in a standardized fashion and is quite costly. Therefore, increased efforts among academic centers, scientific organizations, funding agencies, and industry are necessary to establish improved communication and collaboration.

Design steroid-free monotherapy trials for initial treatment of chronic GVHD (yellow)

Since 2020, only moderate progress has been made in the pursuit of clinical trials for initial

systemic therapy with innovative therapeutic agents in the absence of concurrent glucocorticoid initiation. A single trial enrolled participants with newly diagnosed moderate-severe chronic GVHD for treatment with ibrutinib as monotherapy (NCT04294641), but it only enrolled a limited number of participants. Similarly, the FLIGHT study, a multisite, single-arm, open-label Phase II study investigated oral itacitinib in combination with extracorporeal photopheresis (ECP) in subjects with newly diagnosed moderate to severe chronic GVHD, but was terminated early (NCT04446182).

We acknowledge that while the goal to have steroid-free upfront trials remains worthy, it may have been too ambitious to achieve within 5 years of its recommendation. Progress towards a monotherapy approach is already underway with two ongoing phase 2, open-label, randomized studies which include ruxolitinib monotherapy arms within the trial (NCT06388564, NCT06660355). Other attempts to improve initial therapy include two large phase 3 trials in which a novel agent plus corticosteroids is compared with placebo plus corticosteroids (belumosudil: NCT06143891; axatilimab: NCT06585774).

Limit heterogeneity in clinical trials for treatment beyond first line (yellow)

Until now, organ-specific responses to therapeutic agents have been largely inferred from secondary analyses of larger trial data sets [47–49]. Recent prospective trials are targeting more specific subpopulations of chronic GVHD patients. A single-arm, multicenter phase II trial evaluated ruxolitinib in 47 participants with sclerotic chronic GVHD, demonstrating partial responses in skin and/or joints in 49% at 6 months [50]. Similarly, a single-arm, multicenter phase II trial evaluated ruxolitinib in 49 participants with BOS and demonstrated a lung-specific overall response rate (ORR) of 34.7% (16.3% CR, 18.4% PR), with most responses occurring in mild or moderate disease [51]. Further trials are ongoing in BOS, including an open-label, single-arm, phase II study to evaluate the activity of belumosudil in subjects with new onset of BOS and for subjects with incipient BOS after HCT (NCT05922761). While these trials strive to address the prospective organ-specific data that we lack, such trials can be difficult to enroll and conduct.

Executive summary for WG3: In view of the lower incidence of chronic GVHD as demonstrated by new prevention strategies such as PTCy, ruxolitinib and *ex-vivo* cell manipulations [7,12,52,53], the HCT community will have to be more efficient in addressing unmet clinical needs and gaps of knowledge in the pathophysiology of chronic GVHD. This will also mean that single- or (small) multicenter biology-based trials will be more challenging and costly to perform successfully in the future. The development of alternative trial designs such as platform trials, master protocols, use of common control groups for comparison with novel agents or digital twins for control populations is highly recommended. Clinical trials should focus on improvement of first-line treatment to get more patients off immunosuppression in a shorter period of time. To achieve these important goals and improve treatment, extensive collaboration of academia, industry and patient advocates will be necessary.

WORKING GROUP IV: HIGHLY MORBID FORMS

Daniel Wolff, Sophie Paczesny

Working group IV focused on highly morbid forms of chronic GVHD including sclerosing skin manifestations, ocular and pulmonary disease, and chronic gastrointestinal manifestations [5]. Although severe forms of chronic GVHD have decreased in the last decade along with the overall decrease in chronic GVHD incidence [54], four main areas of need remain: First, studies investigating clinical and biological phenotypes would help understand the evolution of highly morbid forms including the biologic drivers. Second, methods for earlier detection are needed so that effective therapy can prevent severe disability. Better treatment of highly morbid forms has been advanced with 3 agents (belumosudil, ruxolitinib, axatilimab) being FDA approved for treatment of chronic GVHD since 2020. Given their differing mechanisms of action, prospective trials should explore combination treatment [48,55,56]. Third, new trial designs are required for small populations. Last, new primary endpoints for clinical trials in highly morbid forms have not been addressed yet but are still needed, especially in pulmonary and ocular chronic GVHD where stabilization and reduction of symptoms are regarded as a clinical success but not captured by the classic NIH response criteria [57].

Phenotype highly morbid forms of chronic GVHD clinically and biologically (yellow)

Regarding skin sclerosis, longitudinal studies are currently recruiting [41], but cross sectional analyses that have been performed have so far not revealed new targetable pathways [26,58–60]. While these studies described

biology, they lacked characterization of broader patient populations including correlation of biology with specific clinical phenotypes.

Progress in gastrointestinal manifestations of chronic GVHD has focused on ongoing effort to ensure correct classification [61–63]. Diagnostic tools to differentiate GVHD from other causes of GI symptoms are currently being explored including biomarkers [64,65], contrast enhanced ultrasound [66,67], new histopathological markers for alloreactivity [68] and the use of MRI in diagnosis of intestinal GVHD [69]. The generation of experimental and clinical models to address the role of dysbiosis and intestinal inflammation in organ manifestations outside the GI tract is currently ongoing [70]. The collection of blood, stool or other body site samples (e.g. saliva) and GI biopsies in either longitudinal observational cohorts or interventional clinical trials will be used to explore biomarkers. Studies of metabolomic alterations and microbiome compositions with sufficient sampling are currently ongoing in several groups [71–74].

The developing field of spatial transcriptomics may also aid in diagnosis and stratification of these highly morbid forms since cellular interactions in affected tissues may be highly informative.

Use novel trial designs for small populations (red)

No progress has been made for this recommendation. Clinical trials of highly morbid phenotypes continue to use standard study designs which are often underpowered and include heterogeneous populations.

Test new approaches for early identification and treatment of highly morbid forms (yellow)

An area of significant success is the development of new treatment options targeting advanced chronic GVHD, with 3 agents approved for advanced chronic GVHD since 2020 [48,55]. Combination treatment trials of novel agents are just starting (NCT06663722; NCT06388564). Other novel drugs are also being explored [75,76]. Potential synergistic combination treatment should be explored but collaboration between pharmaceutical companies may be required.

For BOS, longitudinal studies are currently recruiting (NCT05250037, NCT05866302) including analysis of risk factors for BOS [32]. Novel longitudinal lung function testing like home spirometry [77], parametric response mapping and Xenon-MRI trials are being explored while a first publication on machine learning showed its utility in early detection of BOS [78]. Biorepositories are currently recruiting with first results expected in 2025. New treatment options being studied including pirfenidone [79], montelukast [80], and ruxolitinib [51] while belumosudil is being studied for upfront treatment of BOS within the BEBOP trial (NCT05922761).

Ocular chronic GVHD remains a challenging organ manifestation due to early nonreversible functional impairment underlining the crucial need for early intervention, which in turn is impaired by the lack of early diagnostic criteria. Unfortunately, while risk factors for ocular chronic GVHD have been established [81,82] the goal of identifying early diagnostic clinical signs and biomarkers has not been accomplished [83]. The ocular group therefore proposed an updated standard of clinical care including prescheduled ophthalmologic visits before start of conditioning and 3 months after transplantation, which should include symptom scoring such as Schirmer's test and conjunctival & corneal staining and an MMP9 concentration in the lacrimal tear fluid [83]. Biomarkers indicating active ocular chronic GVHD have been identified [84]. However, there has been very limited progress on identifying efficacy outcome measures or starting clinical trials targeting ocular chronic GVHD with topical or systemic immunosuppressive agents [85]. Due to the early non reversable changes in ocular chronic GVHD an aggressive upfront approach is proposed which should include anti-inflammatory treatment. The roadmap of the ocular group was updated with the following topics: perform a global randomized longitudinal study using novel imaging and standard tools (like optical coherence tomography (OCT) assessing corneal epithelial thickness) to test regional differences of ocular GVHD acknowledging the crucial role of desiccating stress in induction of ocular chronic GVHD. In addition, randomized trials to try to prevent ocular chronic GVHD are recommended. Finally, the group suggested a revision of the ICD-10 coding since acute GVHD is completely lacking and the NIH coding of ocular chronic GVHD does not reflect recent advances in grading schemes.

Establish primary endpoints for clinical trials addressing highly morbid manifestations (red)

Unfortunately, no significant progress on new methods for response assessment has yet been achieved [5,86,87]. Refinements to response assessment for highly morbid forms are being developed and validated but none are yet ready for deployment.

Executive summary for WG4: The approval of novel agents for more advanced forms of chronic GVHD indicates progress in this area. Studies in phenotype-restricted cohorts are ongoing and should give a better assessment of effectiveness for mono- and combination therapies. However, the lack of measures that can presage highly morbid forms (i.e., skin sclerosis, advanced pulmonary cGVHD) limits our ability to test the benefits of early and effective treatment.

ATYPICAL CHRONIC GVHD TASK FORCE

Geoffrey Cuvelier, Daniel Wolff, Steven Pavletic

During Working Group IV's deliberations in 2020 [5], it was recognized that many suspected chronic GVHD manifestations are not well characterized by the current NIH diagnostic criteria but still result in significant morbidity and mortality [88]. These included chronic GVHD of the hematopoietic system (autoimmune cytopenias), central and peripheral nervous system, kidneys, non-BOS pulmonary disease, atypical features in the musculoskeletal system, polyserositis, and endothelial damage. A subsequent NIH Task Force on atypical chronic GVHD was convened in 2022 [6].

A major challenge is determining whether a clinical manifestation not meeting the NIH chronic GVHD consensus criteria definition is truly caused by alloreactivity (and therefore should be classified as atypical chronic GVHD) versus being related to post-transplant immune dysregulation (potentially also chronic GVHD if autoimmunity or hyperinflammatory), medication side effects, infectious sequelae, a nontransplant related cause, or other etiologies. Such determinations, however, are imperative, given they might influence inclusion / exclusion on clinical trials and inform chronic GVHD therapies. Until pathophysiologic mechanisms are better delineated, atypical chronic GVHD features are likely to remain controversial. Clinicians should consider a broad differential when investigating suspected atypical chronic GVHD features. When describing manifestations with unclear etiologies, the term "possibly related to atypical chronic GVHD" should be used in equivocal situations.

Increase awareness of atypical chronic GVHD in the literature and with clinicians, with proposed case definitions and discussion around challenges with diagnosis of atypical chronic GVHD (yellow)

Since publication of the NIH Task Force manuscript, our understanding of atypical chronic GVHD has increased with publications of case reports and case series [89–96] and emergence of retrospective data about incidence and mortality. Doering et al. reported 16.4% of patients met at least one criterion for atypical chronic GVHD, representing 25% of all chronic GVHD cases. Interestingly, 2.2% of patients exhibited atypical chronic GVHD features only. The most common atypical manifestations included autoimmune cytopenias (24.5%) followed by renal chronic GVHD (13.7%) and polyserositis (13.7%) [97].

The central nervous system (CNS) has also been an organ system with putative atypical chronic GVHD manifestations given high rates of post-transplant neurocognitive impairment and other neurologic syndromes. A multicenter, retrospective clinical study of 66 adult patients with possible CNS acute and chronic GVHD has helped to better delineate this relationship. Specifically, while 57% exhibited MRI changes and 10/12 patients with brain biopsies showed CD3+ and CD163+ parenchymal and perivascular cell infiltration, the clinical, radiologic, and biologic features of CNS GVHD appeared quite variable. While 97% of patients responded initially to immunosuppression, 31% developed recurrent neurologic symptoms, and 1-year overall survival was only 41%, with 67% of survivors exhibiting neurologic sequelae.

With better case definitions and response criteria, future therapeutic clinical trials could include atypical chronic GVHD, ideally with a central study adjudication committee to resolve equivocal cases, similar to what has successfully been done in a previous pediatric chronic GVHD biomarker study [98].

Increase understanding of the incidence, morbidity and mortality from atypical chronic GVHD (yellow)

Although both classical NIH chronic GVHD and atypical chronic GVHD had similarly reduced relapse-related mortality compared to patients without chronic GVHD, nonrelapse mortality was higher in patients with atypical chronic GVHD, primarily driven by restrictive lung disease, renal, and peripheral nervous system subtypes, suggesting these phenotypes are in greatest need of further investigation. Although a larger, prospective and observational natural history study of chronic GVHD that includes monitoring for and description of atypical chronic GVHD along with biological correlates remains an unmet need, no such study has been launched.

Increase understanding of pathophysiology of atypical chronic GVHD (yellow)

New publications describe mouse models of chronic GVHD involving atypical organ systems

[99,100] and biomarkers of endothelial [101,102] and renal [103–105] damage. Diagnostic chronic GVHD biomarkers should adequately differentiate between disease due to chronic GVHD versus other nonchronic GVHD processes. This is particularly important in atypical chronic GVHD, where some uncertainty remains as to whether atypical clinical features are truly related to allo- or autoreactivity or caused by infection, drug-toxicity, natural aging, or pre-existing conditions [6]. For instance the kidney, has long been considered a target organ of chronic GVHD (manifesting as nephrotic syndrome due to membranous nephropathy in approximately 65% of cases), although proving this has been difficult [106]. In 2022, investigators from the Mayo clinic identified a novel glycosylated cadherin protein, protocadherin FAT1, present in the glomerular basement membrane of 14 allogeneic HCT patients with membranous nephropathy [103]. Anti-FAT1 IgG in kidney biopsies and serum of these patients were also discovered, providing an antigen/antibody pathological link. Importantly, this novel antigen appears specific to patients undergoing allogeneic HCT, as FAT1 was not seen in 244 nontransplanted patients with membranous nephropathy from other causes, suggesting a novel antigen with links to allogenic transplant and atypical chronic GVHD. Since the initial report, others have reported similar findings [104,105]. Importantly, protocadherin FAT1 antigen with its apparent specificity after transplant and likely as a renal chronic GVHD biomarker, has been used to differentiate apparent chronic GVHD of the kidney from membranous nephropathy due to chronic nonsteroidal anti-inflammatory drug use [105].

Murine models have also aided in understanding CNS alloreactivity, including a central role for CNS infiltrating donor bone-marrow derived major histocompatibility (MHC)-II+ macrophages [99]. Identical macrophages have been identified in human cerebral cortex tissue after allogeneic HCT [107]. These mouse models have clearly demonstrated an important role for upregulated gene expression associated with interferon-γ responses in CNS chronic GVHD [99], suggesting targeting interferon-γ pathways with JAK1/2 inhibitors such as ruxolitinib or interferon-γ neutralizing antibodies such as emapalumab may be of benefit [100].

Executive summary for atypical chronic GVHD task force

There is an ongoing need for education of clinicians, including primary care physicians and organ specialists, around the manifestations and challenges with diagnosing atypical chronic GVHD. Both basic science and clinical research into atypical chronic GVHD should continue, including further exploration of preclinical models that recapitulate the manifestations with the highest morbidity for patients, such as restrictive lung disease, renal, and central and peripheral nervous systems. Treatment guidelines are needed for atypical chronic GVHD since therapeutic approaches often differ from classic chronic GVHD.

CONCLUDING REMARKS

This document summarizes the six Working Groups' progress since 2020. Despite remarkable therapeutic advances achieved over the last two decades, the implementation of the NIH 2020 consensus goals will need a much more robust execution in years to come given the numerous challenges remaining to address chronic GVHD immune dysfunction and consequent morbidity and mortality. More effective prevention in the current era has made chronic GVHD treatment much more difficult to study because of lower overall incidence as well as different immunological platforms to consider. Intelligent use of the available patient population and application of cutting edge investigative techniques to highly informative biologic samples is even more important. How to approach studying more rare but highly morbid chronic GVHD manifestations poses particular challenges for clinical trial design. Extraordinary effort and dedication of community providers, academia, industry, and advocacy will be needed to most effectively address these challenges and move the research agenda forward.

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SUPPLEMENTARY MATERIALS

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