# Risk biomarkers for chronic graft-versus-host-disease identified

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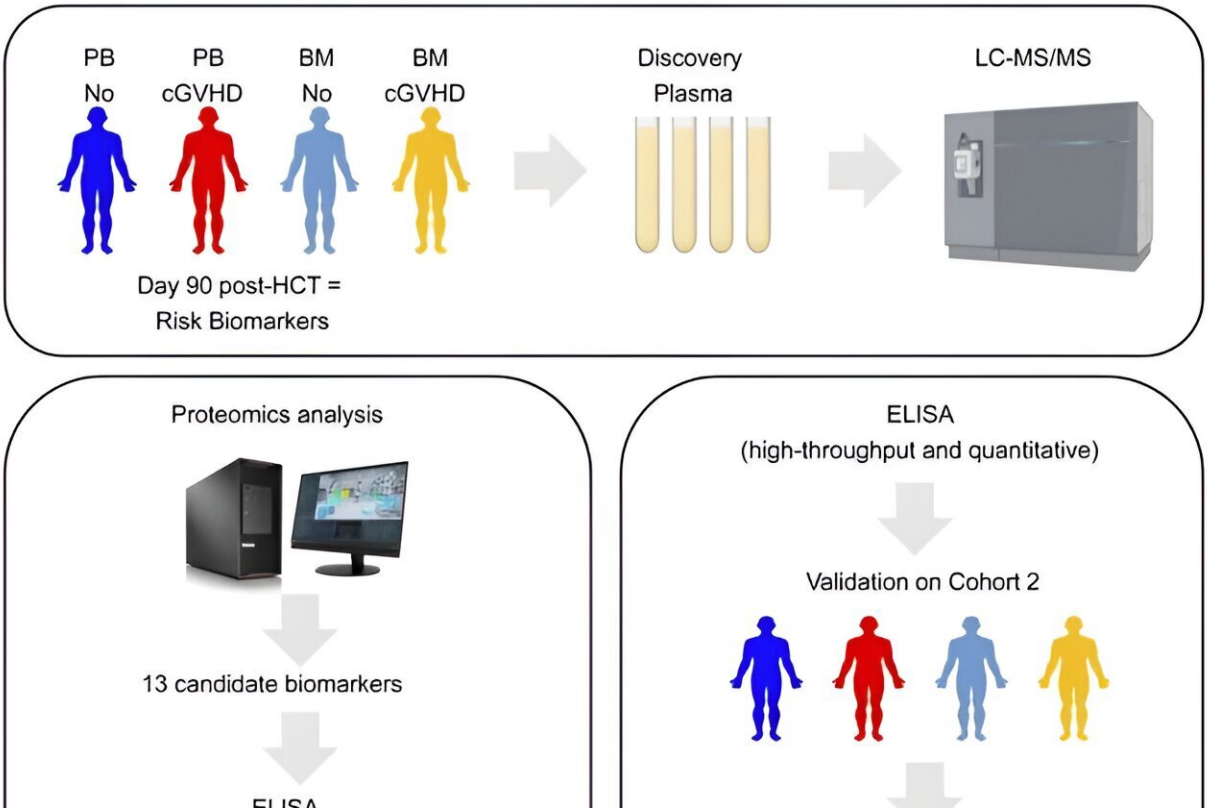


Graphical abstract. Credit: *Journal of Clinical Investigation* (2023). DOI: 10.1172/JCI168575

For someone with a blood cancer, receiving stem cells from a donor offers the possibility of a cure. But patients undergoing this procedure,

called allogeneic hematopoietic cell transplantation, also face the possibility of a common side effect—graft-versus-host-disease (GVHD).

In GVHD, the donated cells start attacking the patient's own healthy cells, believing them to be intruders. Chronic GVHD ranges from mild to severe; unfortunately, it can be quite debilitating and is a major cause of death for patients.

Treatments for chronic GVHD are improving, but it is so prevalent that there is still a strong need to be able to identify patients at most risk of developing this condition so it can be caught and treated early, said MUSC Hollings Cancer Center researcher Sophie Paczesny, M.D., Ph.D.

Paczesny led a multicenter team that reports in the *Journal of Clinical Investigation* that it's identified three risk biomarkers that could be measured at 90 days after transplantation, long before a doctor would be able to make a clinical diagnosis of chronic GVHD.

To her surprise, two of the biomarkers are associated with fibrosis, a hardening or scarring of tissue when it's been over-repaired that shows up as a symptom after the disease is well underway. MMP3 is an enzyme that's involved in lung fibrosing diseases, and DKK3 is a glycoprotein that can promote fibrosis. The third marker that the team identified, CXCL9, is a type of protein that attracts particular immune cells into the organs under attack.

"Usually, you expect more inflammatory markers at day 90," Paczesny said. "You don't expect tissue regeneration markers at this early time point. DKK3 was found before, but really late in chronic GVHD when you have sclerotic disease already, so that's pretty advanced."

This appears to be the first study to show this early measurable increase in fibrotic markers as a sign of potential chronic GVHD, she said.

Chronic GVHD can affect nearly any organ in the body, and the symptoms may be mild, like dry eyes or a rash, or it can progress to involve multiple organs, the joints or the lungs, making it difficult to breath, or sclerosis of the skin. Sclerotic tissue, or tissue where too much connective tissue has been laid down instead of normal tissue, shows up as a hardening and tightening of the skin that limits mobility.

"Current diagnosis is based on clinical signs that may be confirmed by invasive biopsy of skin and appendages, mouth, female genitalia, esophagus, lungs and connective tissues. Unfortunately, these signs often reveal late-stage fibrotic lesions, as opposed to early lesions detected by biomarkers that may be more amenable to treatment," the paper states.

Chronic GVHD can also lead to bronchiolitis obliterans syndrome (BOS), or fibrosis in the lung's small airways. Separately, Paczesny is part of a multicenter team of researchers that published a report in June about the potential for a nasal test to detect early-stage BOS. The nasal test for BOS still requires validation and additional study with a larger group.

The risk biomarkers of chronic GVHD, however, were developed through analysis of samples from almost 1,000 patients from two separate cohorts and validated in a preclinical model.

The samples used in this study were collected between 2004 and 2018. Since then, a new prophylaxis treatment, post-transplant cyclophosphamide (PTCy), has been gaining ground. A phase 3 randomized trial performed through the Blood and Marrow Transplant Clinical Trials Network recently showed that, compared to the standard of care, the new regimen improved GVHD-free, relapse-free survival at one year among patients undergoing allogeneic HLA-matched hematopoietic cell transplant with reduced-intensity conditioning.

The results of that study were published in the *New England Journal of Medicine* and are proposed as the new standard of care for this group of patients. This new regimen did not eliminate GVHD, however, so the need for risk biomarkers still exists. Further, because the patients whose samples were used in her study didn't receive the new regimen, it will be interesting to see how these risk biomarkers appear in patients who do receive the new regimen, Paczesny said.

Paczesny said the next step would be to create an algorithm with a cut-off score designating who should be considered high risk and then to move this into a clinical trial providing preemptive treatment to those who test as high risk.

**More information:** Brent R. Logan et al, Validated graft-specific biomarkers identify patients at risk for chronic graft-versus-host disease and death, *Journal of Clinical Investigation* (2023). DOI: 10.1172/JCI168575

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