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# A reply to Hurley et al. regarding Recipients Receiving Better HLA-Matched Hematopoietic Cell Transplantation Grafts, Uncovered by a Novel HLA Typing Method, Have Superior Survival: A Retrospective Study

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The publication of novel data that challenges current practice initiates important discussions, and we welcome the opportunity to respond to comments received on our article. The central dogma of HLA antigen recognition domain (ARD) matching has been largely brought about by limitations imposed by historical typing technologies. The clinical impact of any additional HLA genetic variation on hematopoietic cell transplantation (HCT) outcome is an important question that, until the recent availability of next-generation sequencing (NGS) technologies, was technically too difficult to answer. The HLA typing landscape is changing, however, with increasing numbers of laboratories moving toward the use of NGS typing platforms and sequencing more of the HLA gene than has been possible previously. With this shift in the available HLA typing information, it is important to determine the clinical relevance of this additional information and to critically evaluate historical practice in light of these changes.

Importantly, we did not claim that our study was the first to identify additional mismatches outside of the ARD in HCT pairs, and we have referenced this appropriately. The novel aspect of our work is our inclusion of these additional regions in the matching algorithm, in conjunction with ARD and noncoding mismatches, as well as HLA-DPB1 matching, -DPB1 T cell epitope matching, and cytomegalovirus serostatus matching. This has enabled increased stratification of outcome risk for patients undergoing unrelated donor HCT for a hematologic malignancy than has been observed using these variables previously. As stated in the Discussion section, we hoped to demonstrate the impact of noncoding variation on HCT outcome, but the low number of cases precluded meaningful clinical analysis; this limitation is fully explained in the article. What was shown is that outcomes for patients receiving grafts from

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donors differing at the noncoding level only were similar to those for patients with donors with any other mismatch.

The authors suggest that parallel testing of the third-generation sequencing platform alongside traditional sequencing methods was necessary to demonstrate accuracy, and they state that there was a high error rate in the original typing. Both statements are incorrect. We did not attempt to demonstrate the accuracy of the method, which has been reported in previous peer-reviewed publications and is an ISO 15189:2012 accredited method. Discrepancies between results of different resolution/generations of HLA typing methods should not be considered errors, but rather should be recognized as stemming from known limitations of historical processes.

We refute the statement that our article "may create confusion and, if not inhibit transplants that occur today based on recommended HLA matching, could delay the identification of donors and delay transplantations where time is of the essence." We clearly noted that this strategy will be particularly advantageous for patients with a choice of many donors, that time to transplantation should be considered, and that current guidelines for donor selection should be followed in cases in which an optimal donor cannot be found.

We absolutely agree with the authors about the need for additional studies to verify our published results, and stated as such. The Center for International Blood and Marrow Transplant Research (CIBMTR) verification study mentioned was submitted as a joint proposal between the CIBMTR and our group. We note that the National Marrow Donor Program, like many other donor registries worldwide, has adopted an extended NGS HLA typing protocol complementary to that described in our study, demonstrating the shift toward typing and matching at this resolution. We question why patients should not be offered the same degree of typing (and thus matching) that is currently applied to donor registers. Finally, it should be noted that previously published data on major histocompatibility complex haplotype matching, coupled with the accepted reduced risk of complications in related donor transplantation, suggest that greater compatibility of the HLA region is associated with better outcome. We also point out that since the acceptance and publication of our article, 2 independent studies (a published manuscript [1] and a presented abstract [2]) have also demonstrated the beneficial effect of matching for additional regions of the HLA gene on unrelated donor HCT outcome, suggesting these observations are not unique, and that there is much still to learn about the impact of genetic variation outside of the ARD on HCT outcome.

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## REFERENCES

1. Vazirabad I, Chhabra S, Nytes J, et al. Direct HLA genetic comparisons identify highly matched unrelated donor-recipient pairs with improved transplantation outcome. *Biol Blood Marrow Transplant*. 2019;25:921–931.
2. De Santis D, Truong L, Witt C, et al. Super high-resolution HLA matching by next-generation sequencing improves the clinical outcomes of haematopoietic stem cell transplantation. *HLA*. 2019;93:276–277.