

Multi-Mismatch Searches in Hap-E Search

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Introduction

In the context of allogeneic hematopoietic stem cell transplantations (HSCT) so-called matching algorithms are used to identify the best matching donor for a patient. As clinical practice evolves, the requirements for donor–recipient matching algorithms must likewise adapt.

To address the increasing use of mismatched unrelated donors (MMUD) in transplantation, we extended our search algorithm Hap-E Search to support higher-level multi-mismatch searches. In the context of this work, a MMUD search is defined as one that returns donors with match grades down to 4/8 (A, B, C, DR) or 5/10 (A, B, C, DR, DQ). Such MMUD searches are meant to complement the already existing standard mismatch searches. For more details on the standard behavior of Hap-E Search, please follow the QR codes to former publications.



Methods

To improve performance and reduce data volume while focusing on clinically meaningful results, we introduce the following constraints for MMUD searches:

- MMUD searches are performed only for **patients** with high-resolution* HLA typing at the relevant search loci (A, B, C, DR for 4/8; A, B, C, DR, DQ for 5/10).
- Only **donors** with high-resolution* HLA typing at the corresponding search loci are included.

→ With these restrictions matching probability calculations are no longer required.

We have evaluated our MMUD search approach on a cohort of one million donors, whose HLA typing distribution is representative of the global DKMS donor pool. Our new MMUD search, down to a match grade of 5/10, was conducted for three sets of 200 patients, with difficult / intermediate / easy searches for which standard searches (10/10) yielded no / 5-19 / 20-99 matching donors, respectively. Donors with a probability > 80% were considered matches in the standard search.

- We call an HLA typing "**high-resolution**" if all contained alleles fall into the same "g" group combining alleles with identical DNA sequences over exons 2 and 3 (including null alleles) with alleles that show synonymous mutations in this region.

Distribution of Search Results

Figure 1: MMUD results for difficult patient searches

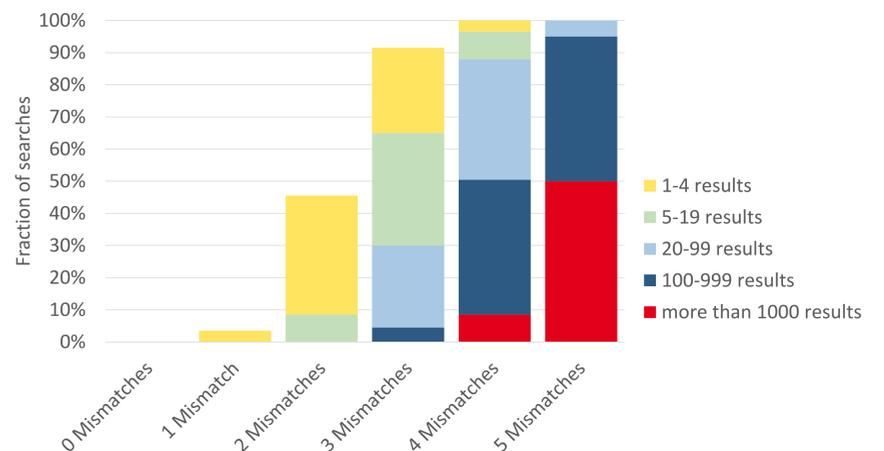


Figure 2: MMUD results for intermediate patient searches

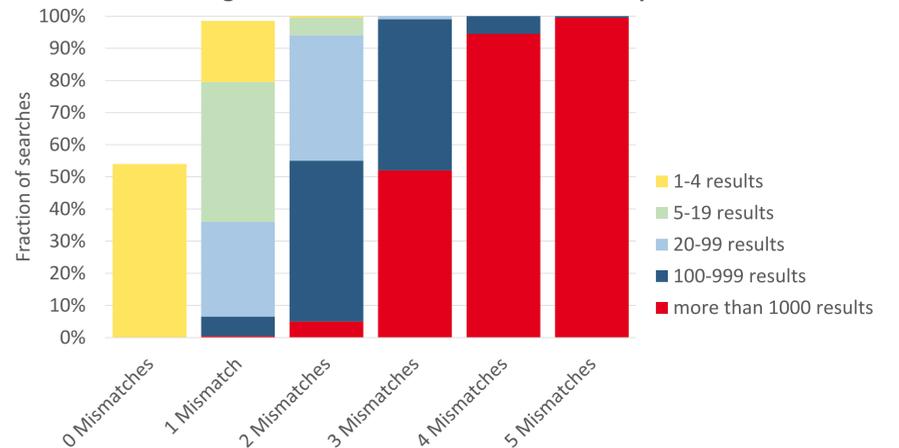
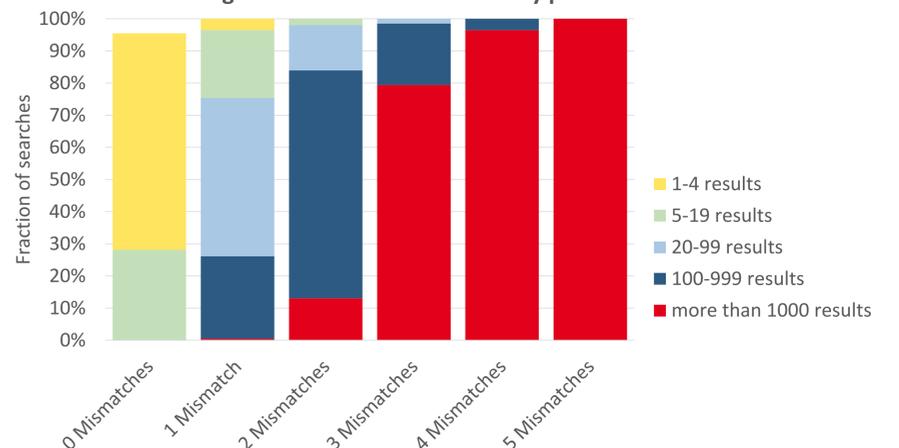


Figure 3: MMUD results for easy patient searches



Results

Figure 1 / 2 / 3 show the distribution of matching high resolution donors per match grade in the MMUD search for the three sets.

Figure 4 shows the duration for the selection of matching donors in the MMUD search colour coded by difficulty of patient searches.

Search set	average / median # 0-2 mismatches	average / median # 3-5 mismatches	Average / median runtime (s)
difficult	3 / 2	884 / 112	8.3 / 8.2
intermediate	115 / 21	10996 / 4804	11.7 / 10.7
easy	209 / 35	16721 / 8947	13.2 / 12.1

Performance

Figure 4: Duration of MMUD donor selection



Average duration of donor selection increases slightly with the number of donors returned, but even searches with more than 100000 results finish within 28 seconds. Donor selection time is expected to scale linearly with the overall number of considered donors. However, we did not evaluate the time needed to prepare search results with additional donor information for transmission and display, which may be affected more severely as the number of results increases.

Conclusion

Rising global demand for MMUD transplantation increases the urgency for robust, scalable matching tools. Hap-E Search's new MMUD approach proves to be a practical, technically efficient new feature. In future, this new capability could be combined with the standard (mismatch) search to provide a comprehensive search result list focusing on clinically relevant results.

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