Use of Intermediate-Resolution Deceased Donor Molecular Typing in Organ Allocation Systems Could Increase the Fraction of HLA-Compatible Donor Offers

MD Shakhaowat Hossain[1], Alyssa Playnter[1], Christopher Frangus[2], MarthaDeConinck[2], Bryan Ray[2], Loren Gragert[1]

1.Division of Biomedical Informatics and Genomics, Deming Department of Medicine, Tulane University School of Medicine, New Orleans, LA, United States.

2. Werfen, Norcross, GA, United States.

Introduction:

The use of sequence-specific oligonucleotide (SSO) methods for HLA typing in deceased donors leads to low-resolution phenotype reporting, creating a burden of information loss for kidney allocation systems and outcome registries. Here, we aimed to measure the potential utility of capturing intermediate-resolution HLA genotypelists instead of antigen-level typing for determining organ offers in allocation systems. Our specific goals include:

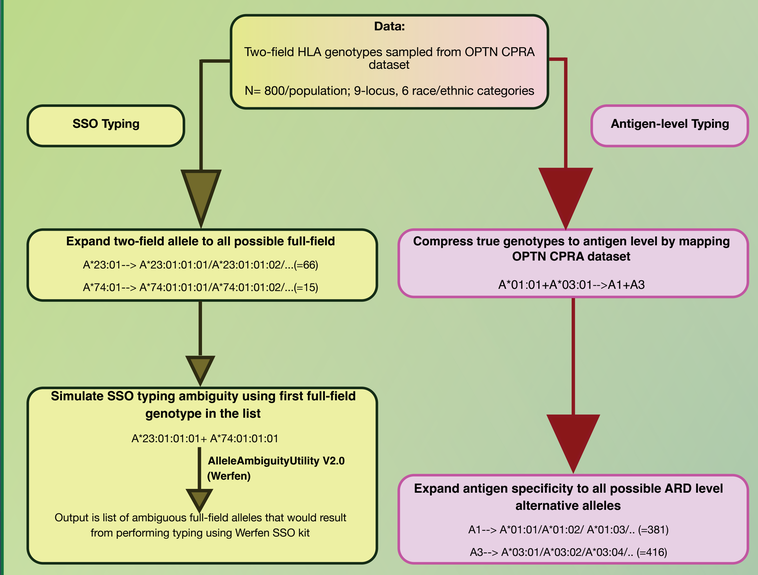
- Create HLA ambiguous genotype list strings from sampled true genotypes simulating SSO typing and antigen level typing.
- Impute High-resolution 9-locus HLA genotypes from the simulated ambiguous typings.
- Measure imputation performance using a calibration curve in a simulated framework where the genotypes are directly sampled from reference population data.
- Calculate Typing Resolution Score (TRS) to measure the uncertainty in the imputed typing.
- Determine the benefits of electronic reporting of SSO typing.
- Evaluate the potential to avoid unnecessary offers of incompatible donors and increase typing resolution for accurate assessment of molecular mismatch and minimize information loss in outcomes registries.

Methods:

- For High-resolution HLA Imputation and uncertainty measurement, we first simulated ambiguous HLA typing by sampling 9-locus two field HLA genotypes data across 6 US race/ethnic groups (n=800/pop) from OPTN CPRA dataset.
- We imputed ambiguous typing using population haplotype frequency and allele frequency data.
- We assessed our imputation model performance with Python Scikit based Validation Framework developed by our lab.
- We measured the level of confidence in resolving ambiguities in the imputed typing by estimating Typing Resolution Score (TRS).

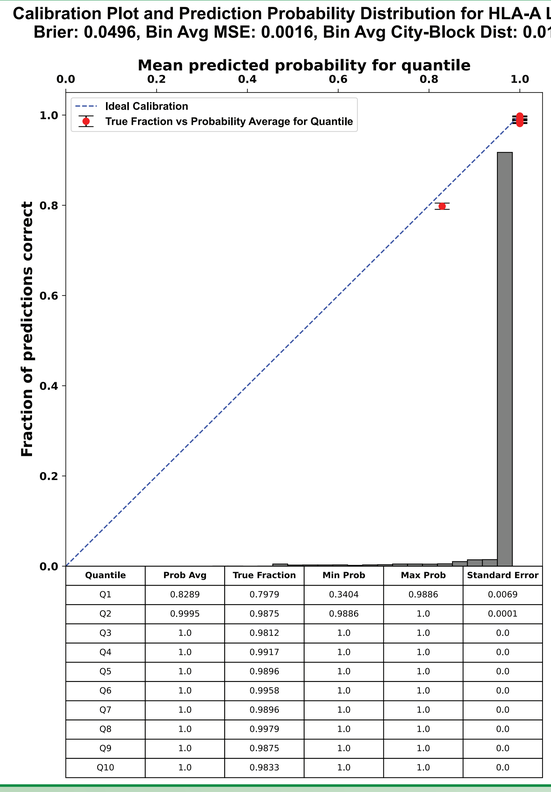
Schematic Diagram of Simulation, Imputation, and TRS Measurement Framework

Simulation of Ambiguous HLA Typing



Simulated HLA typing data are formatted as ambiguous genotype list strings, as presented by Milius et al. (2013).

Results:



Quantile	Prob Avg	True Fraction	Min Prob	Max Prob	Standard Error
Q1	0.8289	0.7979	0.3404	0.9886	0.0069
Q2	0.9995	0.9875	0.9886	1.0	0.0001
Q3	1.0	0.9812	1.0	1.0	0.0
Q4	1.0	0.9917	1.0	1.0	0.0
Q5	1.0	0.9896	1.0	1.0	0.0
Q6	1.0	0.9958	1.0	1.0	0.0
Q7	1.0	0.9896	1.0	1.0	0.0
Q8	1.0	0.9979	1.0	1.0	0.0
Q9	1.0	0.9875	1.0	1.0	0.0
Q10	1.0	0.9833	1.0	1.0	0.0

Figure 1: Calibration of SSO_HaploFreqImpute data using Python Scikit validation framework

- (P120) Profiling performance of high-resolution HLA imputation with complementary metrics and visualizations using an open-source validation framework"
- Details: https://github.com/lgragert/imputation-validation/

Imputation Process

HaploFreqImpute:
Impute ambiguous typing conditional on NMDP population haplotype frequencies and race/ethnic categories - similar method to NMDP HaploStats / HapLogic

Imputation output for Haplotype Frequency

subject_id,rank,hap1,hap2,freq

1588,1,A*02:01~C*16:01~,A*30:01~C*08:02~,0.9897

1588,2,A*02:01~C*16:01~,A*30:01~C*08:02~,0.0099

Use the imputation output to estimate HaploFreqImpute TRS

AlleleFreqImpute:
Impute ambiguous typing conditional on NMDP population allele frequencies and race/ethnic categories - similar method to HLAMatchMaker

Map SSO/antigen-level typing input with population allele frequency and use the filtered data to estimate AlleleFreqImpute TRS

Measurement of Typing Resolution Score (TRS) for Imputation Based on Allele Frequencies (Paunic et al. 2016)

Allele frequencies from Population Database

Allele Frequencies (Locus A):

A*01:01: 0.1

A*02:01: 0.2

Imputed genotypes (A locus)

A*01:01+A*02:01|A*01:01+A*01:01|..

Estimate Genotype Frequency(Hardy-Weinberg Equation):

For A*01:01+A*02:01= 2×0.1×0.2=0.04 (Heterozygous)

For A*01:01+A*01:01= 0.12=0.01 (Homozygous)

Total Genotype Frequency=0.04+0.01=0.05

Estimation of TRS

Estimate Normalized Genotype Frequency:

For A*01:01+A*02:01: 0.04/0.05=0.8

For A*01:01+A*01:01: 0.01/0.05=0.2

TRS=∑p2, where p is a set of normalized genotype frequencies

(0.8)2+ (0.2)2= 0.64+0.04= 0.64

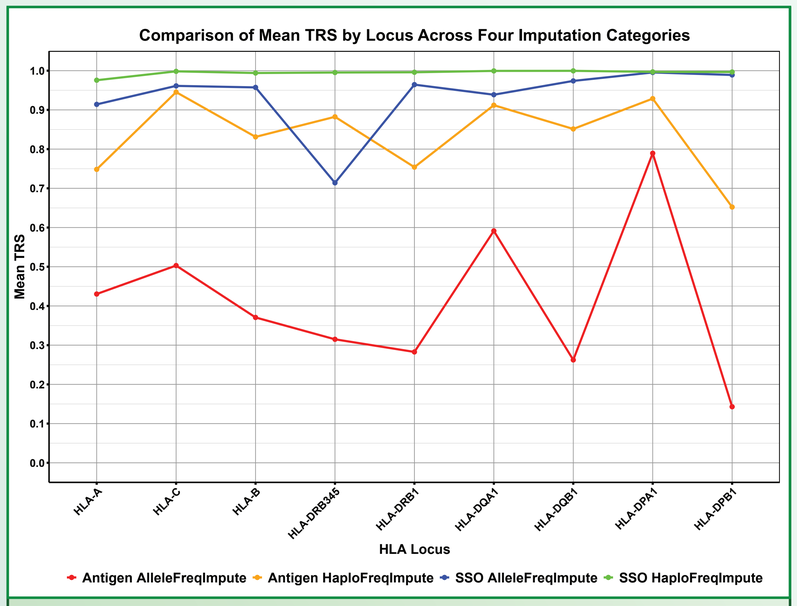


Figure 2: Comparison of mean Typing Resolution Score across different imputation categories

Discussion:

- High Accuracy: Incorrect high-resolution genotype predictions were ≤ 2% for all loci, except the lowest-confidence decile.
- Well-Calibrated: HLA-A locus predictions had a Brier score of 0.0496 and MSE of 0.0016, despite ROC AUC limitations due to class imbalance.
- High Accuracy in SSO Imputation: SSO HaploFreqImpute and SSO AlleleFreqImpute methods consistently achieved high mean TRS (>0.9) across all HLA loci.
- Higher uncertainty: Antigen HaploFreqImpute showed high mean TRS (>0.7) across most loci, while Antigen AlleleFreqImpute exhibited greater variability.

Conclusion:

- There is a greater than 10% likelihood of donor incompatibility conditional on haplotype frequency-based imputation of SSO intermediate resolution typing data and the list of allele-specific unacceptable antigens.
- Implementing allocation offer filters with >90% probability of allele-specific unacceptable antigens would result in minimal loss of HLA-compatible donor offers.
- High-resolution imputation predictions exhibited strong calibration, with low Brier scores and MSE values, confirming the reliability of the imputation method.
- SSO-based imputation approaches showed superior performance in resolving HLA typing ambiguities.
- The US allocation system should implement electronic capture of ambiguous molecular typing data for determining which offers should be made, as alternative (Gragert, L., et al. 2023).

References:

- Gragert, L., et al. (2023). Estimating rates of immunologically incompatible organ offers caused by use of antigen-level deceased donor HLA typing for allocation. Human Immunology, 84 S37-38.
- Milius, R. P., et al. (2013). Genotype list string: a grammar for describing hla and kir genotyping results in a text string. Tissue Antigens, 82(2), 106-112. https://doi.org/10.1111/tan.12150.
- Paunić, V., et al. (2016). Charting improvements in US registry HLA typing ambiguity using a typing resolution score. Human immunology, 77(7), 542–549. https://doi.org/10.1016/j.humimm.2016.05.002.

Contact: MD Shakhaowat Hossain; Email: mhossain1@tulane.edu

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