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Validation of an algorithm to predict the likelihood of an 8/8 HLA-matched unrelated donor at search initiation

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Abstract

A strategy to rapidly determine if a matched unrelated donor (URD) can be secured for allograft recipients is needed. We sought to validate the accuracy of 1) HapLogic™ match predictions, and, 2) a resultant novel Search Prognosis (SP) patient categorization that could predict 8/8 HLA-matched URD(s) likelihood at search initiation. Patient prognosis categories at search initiation were correlated with URD confirmatory typing results. HapLogic™-based SP categorizations accurately predicted the likelihood of an 8/8 HLA-match in 830 patients (1,530 donors tested). Sixty percent of patients had 8/8 URD(s) identified. Patient SP categories (217 Very Good, 104 Good, 178 Fair, 33 Poor, 153 Very Poor, 145 Futile) were associated with a marked progressive decrease in 8/8 URD identification and transplantation. Very Good-Good categories were highly predictive of identifying and receiving an 8/8 URD regardless of ancestry. Europeans in Fair/ Poor categories were more likely to identify and receive an 8/8 URD compared to non-Europeans. In all ancestries, Very Poor and Futile categories predicted no 8/8 URDs. HapLogic™ permits URD search results to be predicted once patient HLA typing and ancestry is obtained dramatically improving search efficiency. Poor-Very Poor-Futile searches can be immediately recognized thereby facilitating prompt pursuit of alternative donors.

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Contributions
Eric Davis, Courtney Byam, and Juliet N. Barker designed and performed the research, and analyzed the data. Sean Devlin analyzed the data. All authors wrote the paper.

Conflicts of Interest
The authors have no relevant conflicts of interest to declare.

Keywords

Allogeneic hematopoietic stem cell transplantation; unrelated donors; search categorization

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Introduction

Allogeneic hematopoietic stem cell transplantation (HSCT) is a potentially curative therapy for many patients with malignant and non-malignant hematologic diseases. However, only 25-30% of potential allograft recipients will have a human leukocyte antigen (HLA)-identical sibling donor. In the absence of a suitable HLA-identical sibling, an 8/8 HLA-A, -B, -C, -DRB1 allele-matched URD has priority as the next best donor option at many centers. This match requirement is consistent with current recommendations[1–3] and is based on multiple single center and registry studies[4-9] including those from Memorial Sloan Kettering Cancer Center (MSKCC)[10].

Unfortunately, most URDs listed on global registries are not typed at high resolution. The need to request samples for confirmatory typing (CT) can cause major delays in proceeding to donor clearance and transplantation especially in patients with difficult searches. This delay can adversely affect transplant outcomes and has special relevance for patients of non-European or mixed ancestries. Such patients due to diverse HLA haplotypes, lesser registry representation, and lower rates of donor availability are far less likely to identify donors who are HLA-matched[11-13]. It can also adversely affect the care of patients in need of urgent transplantation as disease status at the time of transplant is an important determinant of survival in patients with hematologic malignancies (reviewed in Lown et al[14] and references[15-17]). Moreover, patients requiring urgent transplantation are an increasingly larger proportion of transplant service referrals. Consequently, until all donors on global registries can be fully typed at high resolution, a mechanism to rapidly and accurately predict URD search outcome is a significant unmet medical need.

The NMDP facilitates access to potential URDs through their online computer system, Traxis™ and collaborates with volunteer URD registries worldwide. Traxis™ allows transplant centers to request URD DNA samples for either customized typing (individual HLA locus typing) or CT (high resolution typing of all loci of interest). In a preliminary search, after entering a patient's typing, Traxis™ displays two lists of potential URDs. The first list includes the upfront NMDP search result (domestic U.S. and affiliated international registry donors) and the second is the BMDW list (all other international URDs not listed on the upfront NMDP list).

The inclusion of the HapLogic™ matching predictions into the upfront NMDP search was introduced in 2006, and as of 2008 it included the predictions at each of the donor's 8 HLA loci. This technology was further refined in 2011. An example of the resultant chance of the potential donor being an 8/8 (or 10/10) HLA-allele match is shown in Figure 1[18]. The aims of this study were to validate the HapLogic™ 8/8 and individual locus match predictions and a resultant MSKCC Search Prognosis (SP) categorization to permit rapid and accurate prediction of the outcome of URD searches at search initiation prior to donors being requested for CT.

Methods

Patient Population

All patients (n = 830) referred to the Adult Bone Marrow Transplant Service at MSKCC who were 18 years old, diagnosed with a hematologic malignancy or aplastic anemia, and had an URD search performed from 2012-2015 were included in this analysis. Patient ancestry was prospectively obtained from detailed family history as previously described[10]. Patients were categorized into Europeans or non-Europeans, and ancestry subtype (northwestern European, eastern European, southern European, mixed European, African, Asian, Middle Eastern, White Hispanic, or mixed non-European) was also recorded. MSKCC IRB approval was obtained for all data collection and analysis.

Patient Searches

All patients were high resolution HLA-typed prior to commencing the search. At search initiation the results from the upfront NMDP Traxis™ search for each patient were prospectively collected and saved. Specifically, both the HapLogic™ match predictions for each HLA-locus and the predictions of the percentage likelihood of an 8/8 HLA-match for each potential donor were recorded. Up to the top 25 donors were evaluated (if available), but the number recorded and pursued varied according to how good the search was. Donor selection priority for pursuit of a donor sample was based on their likelihood of being an 8/8 HLA-match. After this, donor age was the next criterion with priority being given to younger donor age. Likelihood of donor availability (date of registration/ last contact) and donor center were also major characteristics of importance. Patients with limited donor options also underwent searches through the BMDW list. However, the BMDW list in Traxis does not include HapLogic™ match predictions.

HapLogic™ 8/8 Match Prediction Validation

Eligible URDs were defined as those that had HapLogic™ 8/8 match predictions recorded prior to any HLA typing being resulted, had at least an 1% chance of being an 8/8 match, and had a CT sample obtained and typed without any preceding customized typing requests. Donors who were matched at high resolution were included. These donors are listed as both an 8/8 HLA-match and having a HapLogic match prediction likelihood of 99%. We placed each eligible URD into one of the following groups based on their 8/8 match prediction: 99%, 90-98%, 80-89%, 70-79%, 60-69%, 50-59%, 40-49%, 30-39%, 20-29%, 10-19%, or 1-9%. The number of URDs who were confirmed by CT (once resulted) to be an 8/8 match was subsequently determined, and the frequency of 8/8 HLA-match within each group was compared to that group's 8/8 HLA-match predicted range.

Individual Locus Match Prediction Validation

Eligible loci were those that had HapLogic™ individual locus match predictions recorded prior to any high resolution typing results being obtained and had at least a 1% chance of being a locus match. For loci that had both customized typing and full donor CT completed, only the customized typing result was included. Each eligible locus was placed into groups based on their locus match prediction: 99%, 90-98%, 80-89%, 70-79%, 60-69%, 50-59%,

40-49%, 30-39%, 20-29%, 10-19%, or 1-9%. The number of loci confirmed to be matched within each group was determined, and the frequency of locus match within each group was compared to the group's predicted range.

Categorization of Patient Searches

Patients were placed into one of 6 SP categories devised at MSKCC as outlined in Table 1. The categories (Very Good, Good, Fair, Poor, Very Poor, or Futile) were based on the number of potential 8/8 URDs on a patient's preliminary upfront NMDP search and the corresponding percentage chance of each URD being an 8/8 HLA-match according to HapLogic™. The aim was to segregate patient searches within a spectrum from Very Good to Futile.

Search Outcomes Analysis

Search outcomes were analyzed by SP category and results for European versus non-European patients within each category were compared. The search outcomes examined were: 1) whether the patient had at least one 8/8 URD confirmed by CT (i.e. identified), and, 2) whether the patient proceeded to transplant using an 8/8 URD. The frequency of potential 8/8 URD availability was also examined.

Statistical analysis

The Brier score was used to assess the accuracy of the HapLogic™ 8/8 URD match and the individual locus match predictions. The improvement in the Brier score over a null model where all URD or loci are assigned the same predicted value was assessed using a permutation test. For the locus level prediction, the permutation was done within each donor for each locus. A Fisher's exact test or chi-square test was used to compare identification of or transplantation with an 8/8 URD based on patient SP groups. All analyses were conducted using the R statistical program (R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient Characteristics and Number of Donors Tested

Of the 830 patients studied, there were 558 European patients and 268 Non-European patients with 4 patients having unknown ancestry. European patients (n = 558) included: 170 northwestern Europeans, 150 eastern Europeans, 91 southern Europeans, 144 mixed Europeans, and 3 Europeans (specific sub-group not known). Non-European patients (n = 268) included 44 Asians, 96 Africans, 52 White Hispanic, 17 Middle Eastern, and 59 Mixed Non-European.

Of the 830 patients, 718 (87%) patients had at least one potential 8/8 URD (on the upfront NMDP search or the BMDW list) whereas 112 (13%) did not. The majority of donors were low/ intermediate resolution typed at one or more loci or missing HLA-C. Of the 718 patients with at least one potential 8/8 URD, we pursued 3,432 (4.8 per patient) for CT. Of these, we obtained 2,055 donor samples. Of these 2,055 donor samples, 1,530 had HapLogic™ donor match predictions recorded. The most common reason for not having a HapLogic™ prediction recorded was due to the donor being from the BMDW.

Validation of HapLogic™ 8/8 URD and Individual Locus Match Predictions

The HapLogic™ 8/8 match prediction validation is shown in Table 2 and Figure 2. The 70-79%, 60-69%, and 1-9% URD groups had 8/8-match rates slightly outside of their respective HapLogic™ match prediction ranges at 88%, 53% and 11%, respectively. Otherwise, all other URD groups had frequencies of 8/8-match within their HapLogic™ match prediction ranges. With a Brier score of 0.035, and an associated p-value of < 0.001, there was a strong association between the estimate of the likelihood of 8/8 HLA-match and the percentage match rate for each donor group.

The HapLogic™ match prediction validation for individual loci is displayed in Table 3 and Figure 3. The 70-79% and 40-49% locus groups had a locus match rate slightly higher than their respective HapLogic™ match prediction ranges at 80% and 52%, respectively, whereas the frequencies of individual locus match for all other locus groups were within their HapLogic™ match prediction ranges. Similar to the donor level results, the predictions for individual loci were overall well calibrated (Brier score 0.030, p-value < 0.001).

Donor Identification and 8/8 HLA-Matched URD Transplantation by Patient SP Category and Ancestry

Table 4 demonstrates search outcomes by SP category with each group stratified by patient ancestry. In total, 499 (60%) of 830 patients had   1 identified 8/8 URD. Additionally, 286 (65%) of the 443 patients who had a transplant received an 8/8 URD as the graft source. SP categories from Very Good to Futile demonstrated a decreasing likelihood (100% to 6%) of identifying an 8/8 URD, and a decreasing likelihood (99% to 2%) of receiving an allograft from an 8/8 URD. Search categories Very Good and Good were highly predictive of both identified 8/8 URD and 8/8 URD transplantation regardless of patient ancestry. Notably, Europeans in search categories Fair and Poor were more likely to have 8/8 URDs identified and receive an 8/8 URD transplant compared to non-Europeans. Search categories Very Poor and Futile were highly predictive of no 8/8 URD identified and no transplant with an 8/8 URD. Non-Europeans in the Very Poor and Futile search categories almost never had an 8/8 URD identified and none received an allograft with an 8/8 URD. However, URD access for Europeans in these search categories was also very poor.

Potential 8/8 URD Availability After CT Request By Patient Ancestry

Potential 8/8 URD availability after CT request was stratified by patient ancestry (Table 5). URD availability for Europeans (64%) was greater than that of non-Europeans (48%) (p < 0.001). The ancestry subtypes with the lowest URD availability rates were the White Hispanic (46%), Asian (43%), and African (39%) patients.

BMDW 8/8 URD Search Outcomes by Patient Ancestry for Patients in Poor, Very Poor, or Futile SP Categories

Donor availability by ancestry was analyzed for the patients from the Poor, Very Poor, and Futile SP categories (n = 329) who only had potential 8/8 URD(s) identified via the BMDW list (and none in the NMDP upfront search). Once CT was resulted, Europeans (18/165, 11%) were more likely to have 8/8 URDs identified only via BMDW than non-Europeans (5/164, 3%) (p = 0.008). Furthermore, Europeans in these lower SP categories were more

likely to receive an 8/8 URD allograft facilitated by the BMDW than non-Europeans (10 patients vs none) (p = 0.007).

Discussion

In this analysis we have shown for the first time that utilization of HapLogic™ by a transplant center can provide reliable 8/8 and individual locus HLA-match predictions for URDs. This is compelling support of using HapLogic™ or similar programs to derive an assessment of search prognosis. Furthermore, our SP categories reliably separate patients into a spectrum from nearly guaranteed 8/8 URD to none. Notably, however, search success differed according to patient ancestry within the Fair, Poor, and Very Poor SP categories with access to matched donors being significantly worse in non-Europeans. This is partially explained by potential 8/8 URDs for non-European patients having a worse CT availability rate than those for European patients. These disparities are also due in part to HapLogic™ match predictions only being available for potential 8/8 URDs on the upfront search in Traxis, and Europeans having a higher likelihood than non-Europeans of identifying an 8/8 URD that can only be accessed through the BMDW list. The NMDP is currently working on adding more international registries to their upfront search which in turn would include HapLogic™ match predictions for these donors. In the interim, our findings highlight the validity of HapLogic™ predictions as well as the importance of considering patient ancestry when initially assessing a patient's search and determining the likelihood of obtaining a matched donor.

A notable value of this analysis is that it reflects a large volume of patients with highly diverse ancestries at a large U.S. transplant center. Nonetheless, our findings should be further investigated in even larger patient populations at other centers and in the future could be further refined. A transplant center validation of patient genotype frequency-based search prognostication described by Wadsworth et al[19], and how this compares with our current approach of evaluating the actual searches, is also of interest. In the interim, the findings of the current study have major implications for searches. The SP categorization permits the development of an algorithm to guide search strategy so alternative graft sources (7/8 URDs, cord blood, or haploidentical donors[20,21]) can be immediately pursued in the event that an 8/8 URD will never be identified in the required time period, or is very unlikely. In situations in which a patient has a Fair search, alternative stem cell sources can be evaluated while potential 8/8 URDs are simultaneously requested for additional HLA typing. Conversely, patients with Very Good or Good searches will very likely have at least one 8/8 URD identified regardless of patient ancestry. Thus, pursuit of alternative graft sources and the associated costs may not be necessary unless a search is very urgent.

Overall, the use of this algorithm has dramatically improved search efficiency at our center as it has facilitated efficient patient triage to cord blood or haplo-identical donor transplantation in the absence of an 8/8 matched URD, or the acceptance of a 7/8 HLA-matched URD. This can speed access to transplant and almost guarantees a donor for all patients. This approach can also facilitate cost savings from streamlining the process. Optimal efficiency of this approach to searches is contingent upon: 1) a clearly accepted

definition of urgency and time frame for transplantation and 2) what alternative graft source is the priority (and available) if an 8/8 URD is not feasible in the required time period.

Recognition of futile searches should provide robust evidence that would argue against waiting for donors that will never likely eventuate. Our findings have major relevance to centers who would prefer to use an alternative donor (haplo-identical or cord blood) if a matched URD cannot be secured. Furthermore, the institution of alerts to transplant centers early in the search process notifying them of the search prognosis is appropriate, especially in difficult searches. Additionally, our data would also strongly argue against conducting futile donor drives that will not help the patient. At the very least the patient and family should be informed that such donor drives will have negligible impact on their search success if the search has already shown to be very poor or futile. That only two-thirds of donors for European patients and less than half for those of Asian, African and white Hispanic patients are available for CT should also be recognized. This is especially important to efficiently triage search strategy to successful alternative donors.

Acknowledgments

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Highlights

- HapLogic™ provides reliable 8/8 and individual locus HLA-match predictions for unrelated donors (URDs).

- A novel Search Prognosis patient categorization can accurately predict 8/8 HLA-matched URD likelihood at search initiation.

- Rapid recognition of poor, very poor or futile searches can facilitate immediate pursuit of alternative graft sources.
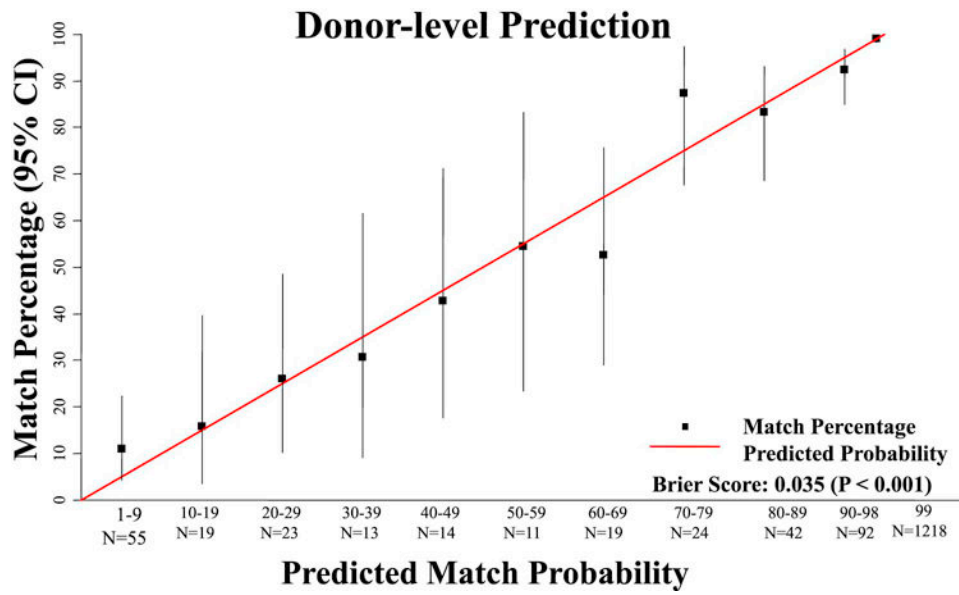
8/8 Match Prediction

	A	B	C	DRB1	DQB1	DRB3/4/5	Pr(n) of 10	Pr(n) of 8
	02:XEVZ	15:SNFF	07:ET	11:04	03:01		10/10=99%	8/8=99%
	03:VSBE	18:TXYF	07:JECH	13:02	06:04		9/10=99%	7/8=99%
	P	P	P	A	A		8/10=99%	6/8=99%
	P	P	P	A	A			
	99%	99%	99%	99%	99%			

Individual Locus Match Prediction

	A	B	C	DRB1	DQB1	DRB3/4/5	Pr(n) of 10	Pr(n) of 8
	01:GNZB	08:GMHM		03:01			10/10=64%	8/8=87%
	68:DYRX	58:DKR		07:01			9/10=99%	7/8=99%
	P	P		A			8/10=99%	6/8=99%
	P	P		A				
	99%	99%	87%	99%	95%			

Figure 1. Examples of HapLogic™ Match Predictions
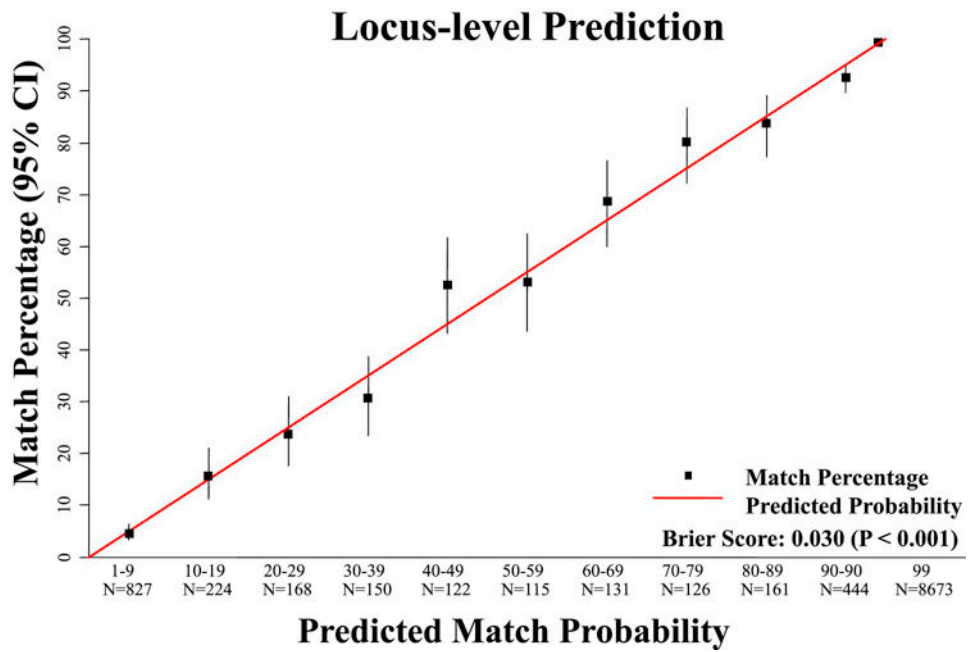These examples were obtained from the NMDP Traxis™ system.

Figure 2. Validation of the accuracy of Haplogic™ donor predictions
This figure shows a highly significant correlation between the predicted 8/8 HLA-match probability and the result of the donor CT.

Figure 3. Validation of the accuracy of Haplogic™ HLA-locus predctions
This figure shows a highly significant correlation between the predicted locus HLA-match probability and the result of the high resolution locus CT.

Table 1

SP Category Definitions

SP Category	Chance of Matching at 8 Alleles[*]
Very Good	20 8/8 donors with a 85% chance
Good	5-19 8/8 donors with a 85% chance
	20 8/8 donors with a 70% chance
Fair	1-4 8/8 potential donors with 85% chance
	1-19 8/8 potential donors with 70% chance
	5 8/8 potential donors with a 40-69% chance
Poor	1-4 8/8 potential donors with 40-69% chance
	1 8/8 potential donor with 25-39% chance
Very Poor	1 8/8 potential donor with 24% chance
Futile	0 8/8 potential donors

[*] percentage likelihoods according to HapLogic™ 8/8 match predictions.

Table 2

HapLogic™ 8/8 Match Prediction Validation, N = 1,530 URDs

Prediction: Chance of 8/8 Match	N URDs Tested	CT Result: N (%) URDs 8/8 Matched
99%	1218	1,207 (99%)
90 – 98%	92	85 (92%)
80 – 89%	42	35 (83%)
70 – 79%	24	*21 (88%)* [*]
60 – 69%	19	*10 (53%)* [*]
50 – 59%	11	6 (55%)
40 – 49%	14	6 (43%)
30 – 39%	13	4 (31%)
20 – 29%	23	6 (26%)
10 – 19%	19	3 (16%)
1 – 9%	55	*6 (11%)* [*]

[*]
Result for URD group out of predicted range.

Table 3

HapLogic™ Individual Locus Match Prediction Validation, N = 11,141 Loci

Prediction: Chance of Locus Match	N Loci Tested	CT Result: N (%) Loci Matched
99%	8673	8627 (99%)
90 – 98%	444	411 (93%)
80 – 89%	161	135 (84%)
70 – 79%	126	*101 (80%)**
60 – 69%	131	90 (69%)
50 – 59%	115	61 (53%)
40 – 49%	122	*64 (52%)**
30 – 39%	150	46 (31%)
20 – 29%	168	40 (24%)
10 – 19%	224	35 (16%)
1 – 9%	827	38 (5%)

*
Result for locus group out of predicted range.

Table 4

SP Category and Patient Ancestry* by Search Outcome, N = 830 Patients

SP Category by Patient Ancestry	N Patients	N (%) with Identified 8/8 URD	Patient Ancestry p-value	N Received Transplant	N (%) Transplants with 8/8 URD	Patient Ancestry p-value
Total:	**830**	**499 (60%)**	—	**443**	**286 (65%)**	—
Very Good	**217**	**217 (100%)**	—	**137**	**135 (99%)**	—
European	188	188 (100%)	N/A	119	118 (99%)	0.235
Non-European	28	28 (100%)		17	16 (94%)	
Good	**104**	**104 (100%)**	—	**67**	**64 (96%)**	—
European	86	86 (100%)	N/A	55	53 (96%)	0.452
Non-European	18	18 (100%)		12	11 (92%)	
Fair	**178**	**136 (76%)**	—	**87**	**69 (79%)**	—
European	119	97 (82%)	0.024	60	52 (87%)	0.018
Non-European	58	38 (66%)		26	16 (62%)	
Poor	**33**	**16 (48%)**	—	**17**	**10 (59%)**	—
European	19	14 (74%)	0.001	12	10 (83%)	0.003
Non-European	14	2 (14%)		5	0 (0%)	
Very Poor	**153**	**18 (12%)**	—	**71**	**7 (10%)**	—
European	89	15 (17%)	0.024	50	7 (14%)	0.180
Non-European	63	3 (5%)		20	0 (0%)	
Futile	**145**	**8 (6%)**	—	**64**	**1 (2%)**	—
European	57	6 (11%)	0.058	30	1 (3%)	0.476
Non-European	87	2 (2%)		33	0 (0%)	

*
4 patients had missing ancestry information and are included according to their Search Prognosis category result but could not be included in the sub-analysis of European versus non-European patients within each group.

Table 5

Potential 8/8 URD Availability After CT Request Stratified by Patient Ancestry [*], N = 3,353 URDs

Patient Ancestry	N URDs Pursued for CT For Each Patient Group [*]	N URDs Available for CT	Patient Ancestry p-value
Total:	**3,353**	**2,040 (61%)**	—
European (n = 558 patients)	*2,618*	*1,682 (64%)*	*< 0.001*
Non-European (n = 268 patients)	*726*	*352 (48%)*	
Ancestry Subtype	—	—	—
NW European	*869*	*575 (66%)*	—
Eastern European	*793*	*498 (63%)*	—
Southern European	*277*	*186 (67%)*	—
European Mix	*672*	*413 (61%)*	—
Asian	*166*	*71 (43%)*	—
African	*148*	*58 (39%)*	—
White Hispanic	*193*	*89 (46%)*	—
Middle Eastern	*47*	*31 (66%)*	—
Mixed Non-European	*175*	*109 (62%)*	—

[*] 9 URDs were excluded from the European versus non-European analysis as the European versus non-European ancestry was not determined for 4 patients. Also, 13 URDs were excluded from ancestry subtype analysis due to undetermined ancestry subtype in a total of 7 patients.