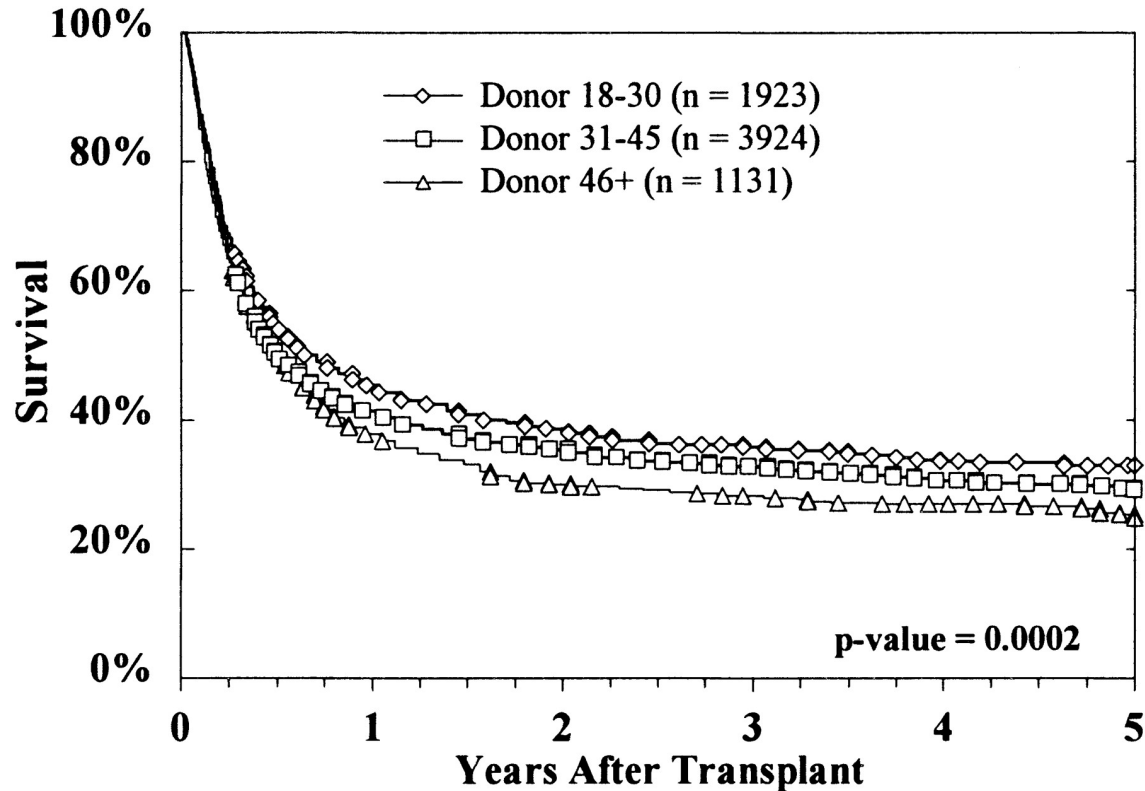


Is the Youngest Donor Always the Best Choice to Optimize Outcomes for Matched Unrelated Allogeneic Transplant?

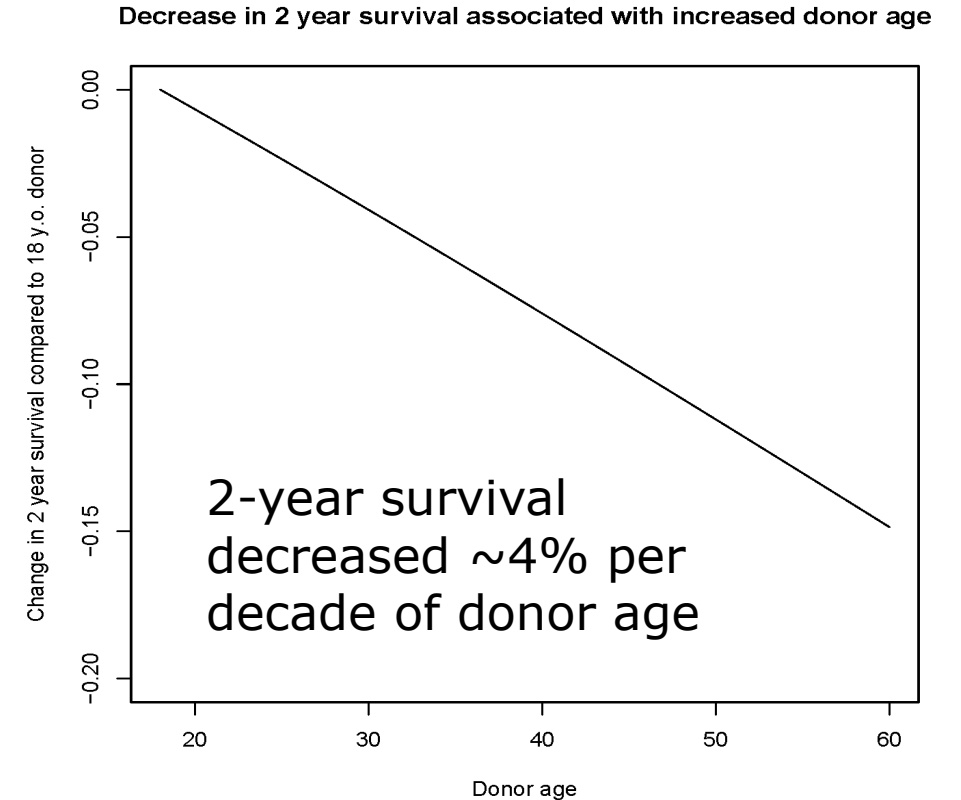
Improving Precision Using Novel Statistical Machine Learning

Steven M. Devine, Rodney A. Sparapani, Martin J. Maiers, Stephen R. Spellman, Bronwen E. Shaw, Purushottam W. Laud, Caitrin Bupp, Meilun He and Brent R. Logan

Increasing donor age impacts survival



Kollman et al. Blood 2001



Shaw et al, BBMT, 2018

Background

- Our previous work found that the youngest donor was the optimal choice
- Strengths of the prior analysis:
 - Large sample size: trained on 10,318 patients
 - Novel methodology: machine learning regression by Bayesian Additive Regression Trees
- Limitations of the prior analysis:
 - Only considered a composite dichotomous outcome
 - Either death or acute GVHD grades 3 and 4
 - Short-term outcomes of only 180 days
 - Historical dataset: 1999 to 2014

original reports

Optimal Donor Selection for Hematopoietic Cell Transplantation Using Bayesian Machine Learning

Brent R. Logan, PhD^{1,2}; Martin J. Maiers, MS³; Rodney A. Sparapani, PhD¹; Purushottam W. Laud, PhD¹; Stephen R. Spellman, MBS³; Robert E. McCulloch, PhD⁴; and Bronwen E. Shaw, MD, PhD²

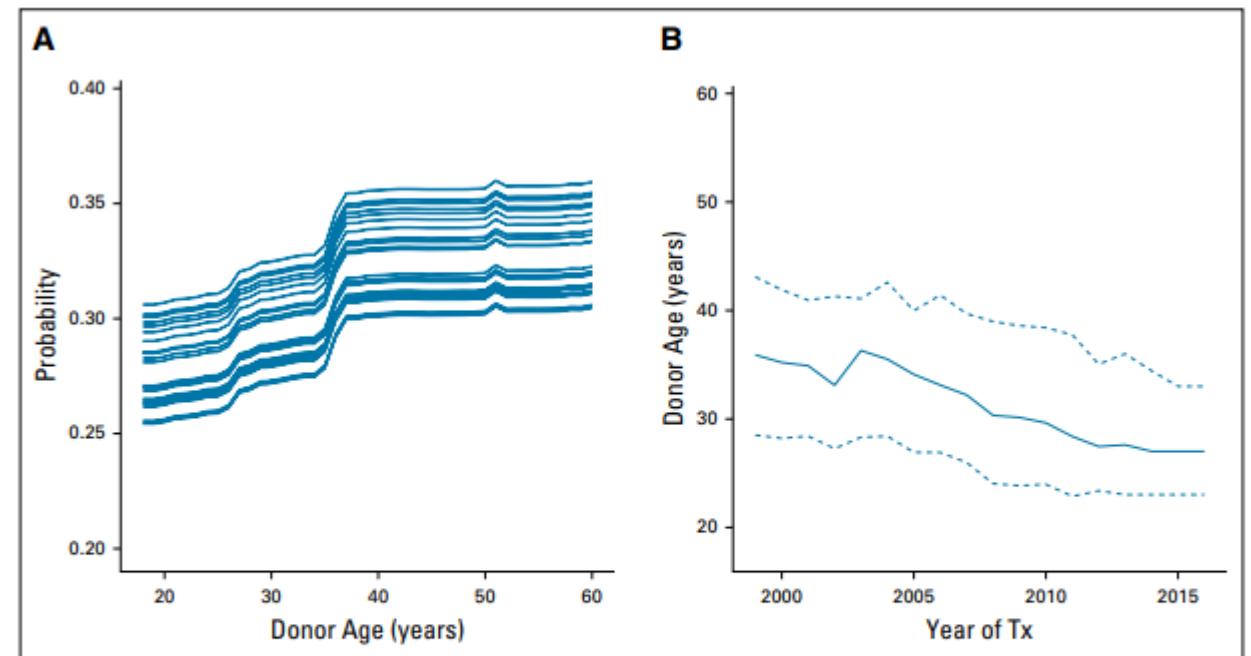


FIG 1. Donor age effect on outcome. (A) Risk of acute GVHD grade 3 or 4 or death by 180 days versus donor age, for 40 different risk profiles of patient characteristics known at the time of search initiation, specifically recipient age (18-29, 30-39, 40-49, 50-59, and 60+), sex, and disease (AML, ALL, CML, and MDS). Predictions come from the BART model on the training data and are averaged over the distribution of other patient, disease, and transplant characteristics in the training cohort. (B) Donor age (median and quartiles) versus year of transplant in combined training and validation data sets. ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; BART, Bayesian Additive Regression Trees; CML, chronic myeloid leukemia; GVHD, graft-versus-host disease; MDS, myelodysplasia; Tx, transplant.

Study Methods

- Updates to address limitations of prior analysis:
 - Considered 2 time-to-event outcomes separately along with their tradeoffs
 - Overall survival (OS)
 - Event-free-survival (EFS): death, relapse, graft failure/rejection or moderate/severe chronic GVHD
 - Evaluated **3-year** rather than 180-day outcomes
 - Used a more contemporary dataset including HCTs from 2016 to 2019
 - Trained on a large sample of 10,016 patients
 - More advanced machine learning regression methodology based on our latest work Nonparametric failure time (NFT) Bayesian additive regression trees (BART)
 - Sparapani et al. Nonparametric failure time: Time-to-event machine learning with heteroskedastic Bayesian additive regression trees and low information omnibus Dirichlet process mixtures. Biometrics 2023

Study Cohort

- CIBMTR cohort of all first US alloHCT from 2016 to 2019
- Malignant and non-malignant diseases
- **Matched** unrelated donors
 - 8/8 high-resolution matching of HLA at A, B, C, DRB1
- Considered the following donor factors for optimal matching
 - Age
 - sex/parity
 - CMV status
 - Other HLA loci: DQB1 and DPB1 permissive matching

Analysis approach

- Randomly split into training (85%, N=10,016) and validation (15%, N=1,802)
 - Evaluated donor factors and influence on OS and EFS
 - **Defined a Zone of Indifference for clinical significance (<1%)**
 - **Factors associated with a >1% significant impact on 3-yr OS or EFS retained**
- Donor optimization using the NMDP Search Archive (N=699)
 - Complete listing of donors at the time of recipient's search
 - Identification of alternative donors with a $\geq 90\%$ likely 8/8 match

Analysis approach

- Using search archive data, we examined three optimal strategies for donor selection
 - OS only
 - EFS only
 - 2:1 weighted average of OS and EFS respectively (denoted OS2:EFS1)
 - Prioritizes OS while considering EFS when the difference in OS predictions between potential donors is minimal
- Predicted OS and EFS calculated for each patient under all three optimal donor strategies benchmarked by the actual donor used for the transplant, i.e., better unless optimal donor was the actual

Population Characteristics - Recipients

	Training Cohort N=10006	Validation Cohort N=1802	Search Archive Cohort N=699	Total Cohort
	N (%)	N (%)	N (%)	N (%)
Recipient Age				
0-19	1159(11.6%)	179(9.9%)	73(10.4%)	1338(11.3%)
20-39	1470(14.7%)	255(14.2%)	112(16.0%)	1725(14.6%)
40-59	3167(31.6%)	537(29.8%)	200(28.6%)	3704(31.3%)
60-82	4220(42.1%)	831(46.1%)	314(44.9%)	5051(42.7%)
Recipient Sex				
Male	5828(58.2%)	1059(58.8%)	401(57.4%)	6887(58.3%)
Recipient Race				
White	8993(93.0%)	1619(92.8%)	636(94.2%)	10612(93.0%)
Black	307(3.2%)	57(3.3%)	17(2.5%)	364(3.2%)
Asian	281(2.9%)	56(3.2%)	15(2.2%)	337(3.0%)
Other	86(0.9%)	13(0.7%)	7(1.0%)	99(0.9%)
Missing	349	57	24	406
Recipient Ethnicity				
Hispanic	764(7.9%)	143(8.3%)	55(8.2%)	907(8.0%)
Missing	359	81	30	440

Most recipients non-Hispanic White

Population Characteristics - Donors

	Training Cohort N=10006	Validation Cohort N=1802	Search Archive Cohort N=699	Total Cohort
Donor age				
17-29	6499(65.4%)	1176(65.7%)	479(68.6%)	7675(65.4%)
30-39	2291(23.0%)	411(22.9%)	146(20.9%)	2702(23.0%)
40-49	855(8.6%)	148(8.3%)	52(7.4%)	1003(8.5%)
50-60	296(3.0%)	56(3.1%)	21(3.0%)	352(3.0%)
Missing	75	11	1	86
Donor parity				
Male	6985(70.2%)	1245(69.4%)	524(75.1%)	8230(70.0%)
Female-nulliparous	1886(18.9%)	370(20.6%)	137(19.6%)	2256(19.2%)
Female-parous	1086(10.9%)	179(10.0%)	37(5.3%)	1265(10.8%)
Missing	59	8	1	67
Sex match				
Yes	5751(57.8%)	1032(57.5%)	408(58.5%)	6783(57.7%)
Missing	59	8	1	67
CMV match				
Yes	5560(55.8%)	990(55.4%)	395(57.2%)	6550(55.8%)
Missing	54	16	8	70
DQB1 match				
Yes	9377(95.6%)	1699(95.8%)	667(96.8%)	11076(95.6%)
Missing	206	29	10	235
DPB1 match or permissive mismatch				
Yes	6430(75.4%)	1171(76.3%)	444(73.6%)	7601(75.5%)
Missing	1490	267	96	1757

Most donors <age 40 and majority male

Population Characteristics - Transplant

	Training Cohort N=10006	Validation Cohort N=1802	Search Archive Cohort N=699	Total Cohort
Graft type				
Bone marrow	2239(22.4%)	384(21.3%)	158(22.6%)	2623(22.2%)
Peripheral blood	7777(77.6%)	1418(78.7%)	541(77.4%)	9195(77.8%)
Karnofsky score				
≤60	144(1.5%)	25(1.4%)	9(1.3%)	169(1.5%)
70	1268(12.9%)	222(12.6%)	91(13.2%)	1490(12.9%)
80	2896(29.5%)	557(31.6%)	226(32.8%)	3453(29.8%)
90	3971(40.5%)	701(39.7%)	257(37.4%)	4672(40.4%)
100	1528(15.6%)	259(14.7%)	105(15.3%)	1787(15.4%)
Missing	209	38	11	247
Disease				
AML	3956(39.5%)	746(41.4%)	290(41.5%)	4702(39.8%)
ALL	1290(12.9%)	251(13.9%)	102(14.6%)	1541(13.0%)
MDS	1988(19.8%)	362(20.1%)	139(19.9%)	2350(19.9%)
Other	2782(27.8%)	443(24.6%)	168(24.0%)	3225(27.3%)
Disease Stage (ALL, AML, MDS only)				
	6947	1306	505	8253
Early	4159(59.9%)	775(59.3%)	279(55.2%)	4934(59.8%)
Intermediate	1360(19.6%)	261(20.0%)	99(19.6%)	1621(19.6%)
Advanced	1428(20.6%)	270(20.7%)	127(25.1%)	1698(20.6%)
Missing	287	53	26	340

Majority of grafts were PBSC

Population Characteristics - Transplant

	Training Cohort N=10006	Validation Cohort N=1802	Search Archive Cohort N=699	Total Cohort
Conditioning Regimen				
Myeloablative	4974(49.7%)	885(49.1%)	364(52.1%)	5859(49.6%)
Non-myeloablative	1122(11.2%)	213(11.8%)	77(11.0%)	1335(11.3%)
Reduced intensity	3920(39.1%)	704(39.1%)	258(36.9%)	4624(39.1%)
GVHD prophylaxis				
Cyclophosphamide	1130(11.3%)	216(12.0%)	49(7.0%)	1346(11.4%)
FK506+MMF	1097(11.0%)	209(11.6%)	89(12.7%)	1306(11.1%)
FK506+MTX	5425(54.2%)	965(53.6%)	377(53.9%)	6390(54.1%)
FK506 only	1020(10.2%)	196(10.9%)	82(11.7%)	1216(10.3%)
Other	1344(13.4%)	216(12.0%)	102(14.6%)	1560(13.2%)
HCT-Comorbidity Index				
0	2093(21.1%)	333(18.7%)	135(19.5%)	2426(20.7%)
1 to 2	2938(29.6%)	547(30.6%)	215(31.0%)	3485(29.7%)
3 to 4	3050(30.7%)	539(30.2%)	203(29.3%)	3589(30.6%)
5+	1851(18.6%)	366(20.5%)	141(20.3%)	2217(18.9%)
Missing	84	17	5	101
Transplant year				
2016	2347(23.4%)	419(23.3%)	336(48.1%)	2766(23.4%)
2017	2527(25.2%)	438(24.3%)	324(46.4%)	2965(25.1%)
2018	2593(25.9%)	450(25.0%)	33(4.7%)	3043(25.7%)
2019	2549(25.4%)	495(27.5%)	6(0.9%)	3044(25.8%)

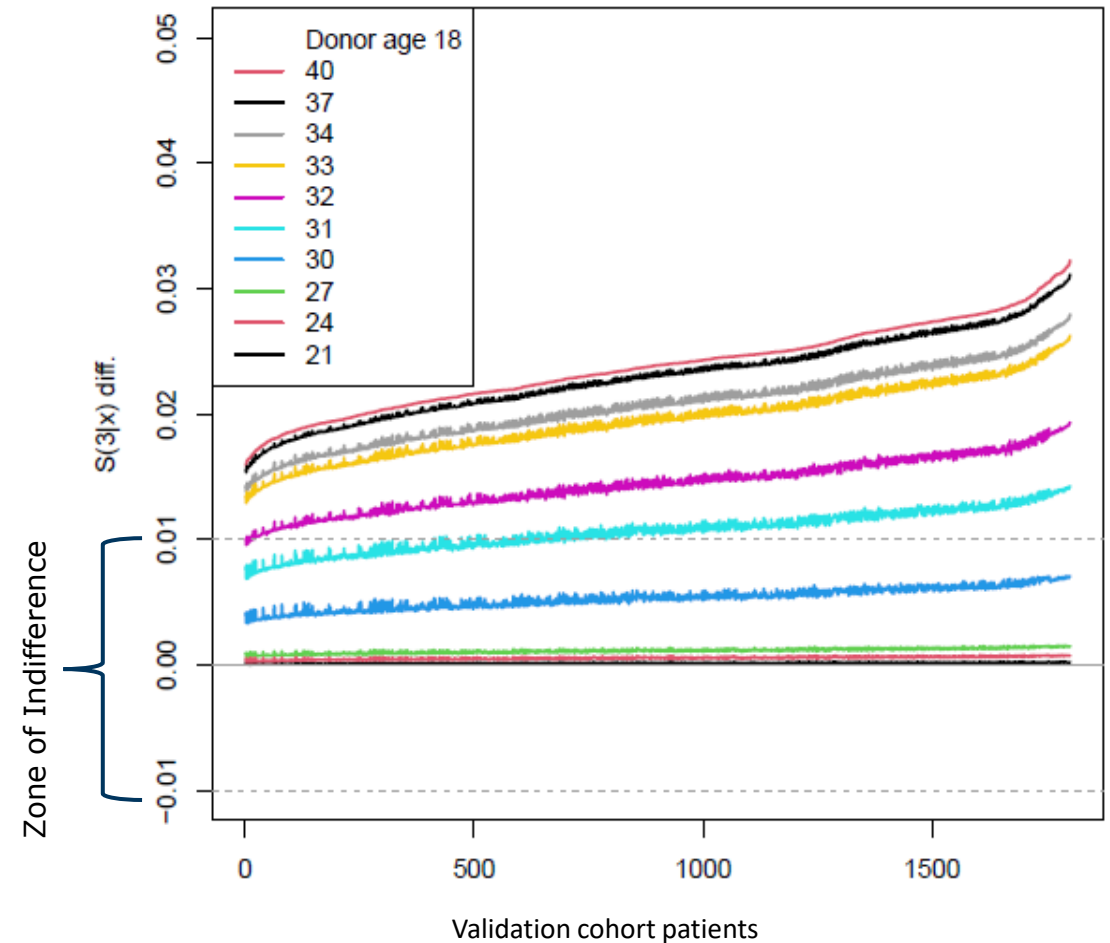
PTCy-based only ~11% of total

Results

- Donor parity, CMV status, HLA-DQB1 matching and HLA-DPB1 permissive matching were **not** associated with >1% improvements in OS or EFS at 3 years
- Only donor age (for OS and EFS) and sex (for EFS) had clinically important impacts on outcomes and were considered for donor optimization
- **Donor age impacts**
 - Donor age is more important for OS than EFS
 - Generally, younger donors 18 to 30 are optimal
- **Donor sex impacts**
 - Very little, if any, impact on OS
 - Strong impact on EFS with a preference for Male donors (probably due to less cGVHD)

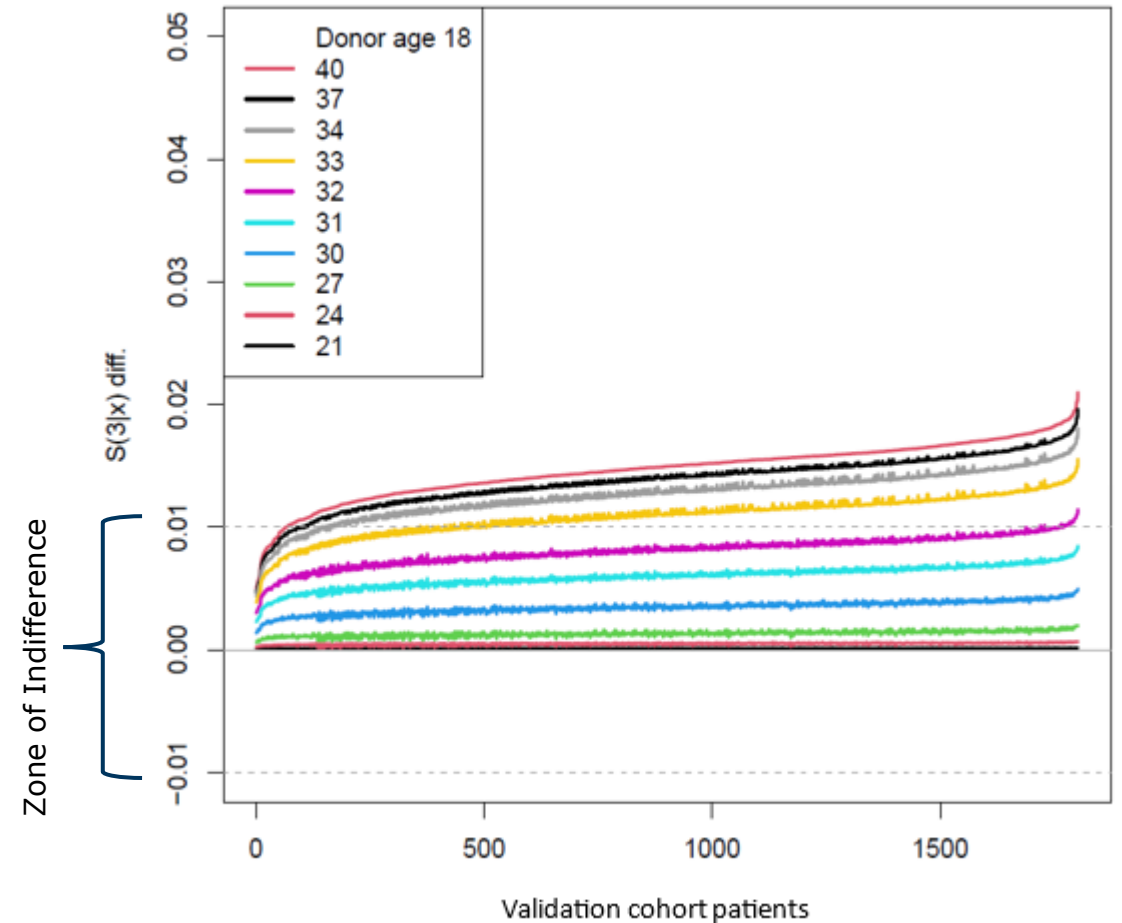
Impact of Donor Age on OS

- Waterfall plot of predicted OS differences at 3 years post-transplant for an 18-year-old vs. an older donor from the validation cohort.
- Compared to donors ≥ 31 , an 18-year-old is associated with a substantial increase in OS where all recipient OS differentials > 0.01
- Compared to donors 21 to 30, an 18-year-old choice produces benefits that are negligible and fall within the Zone of Indifference.



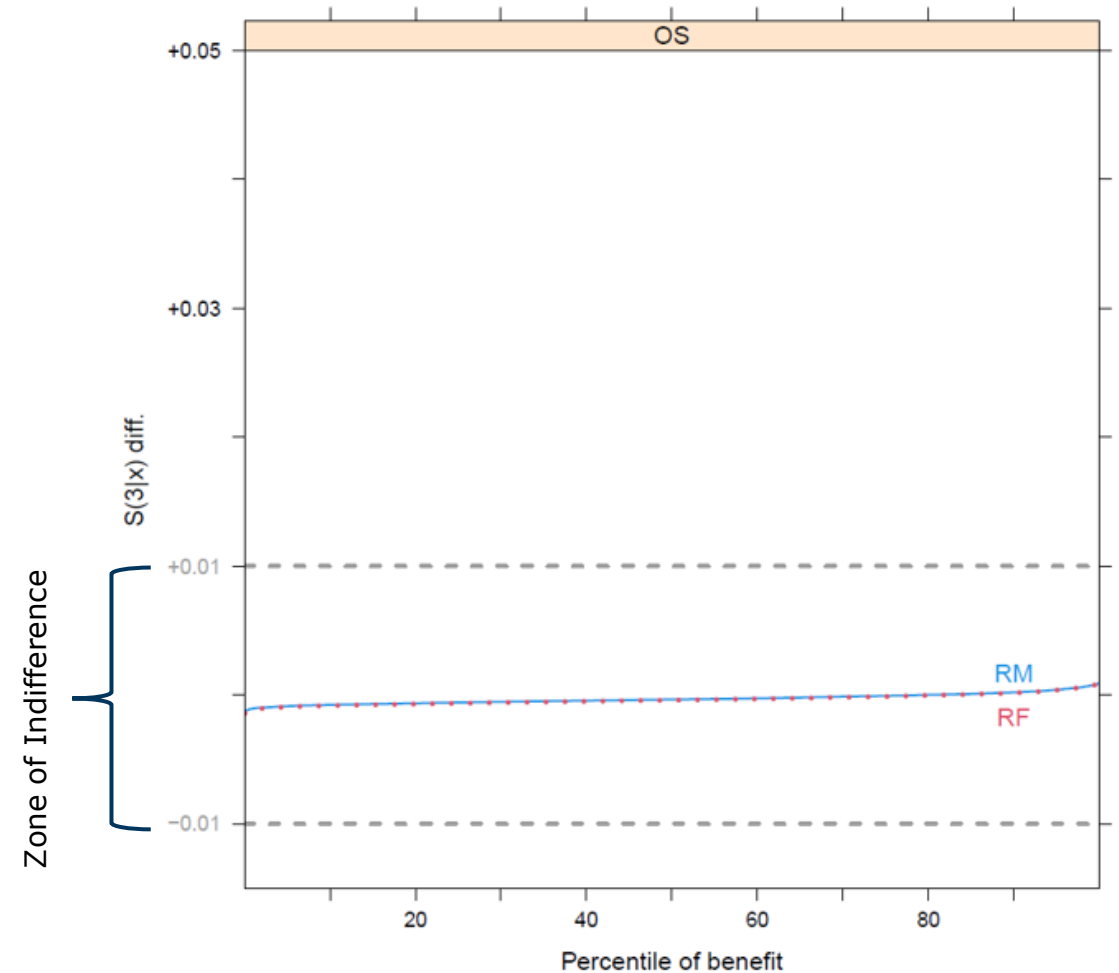
Impact of Donor Age on EFS

- Waterfall plot of predicted EFS differences at 3 years post-transplant for an 18-year-old vs. an older donor from the validation cohort.
- Compared to donors ≥ 33 , an 18-year-old is associated with a substantial increase in EFS where all recipient OS differentials > 0.01
- Compared to donors 21 to 32, an 18-year-old choice produces benefits that are negligible and fall within the Zone of Indifference.



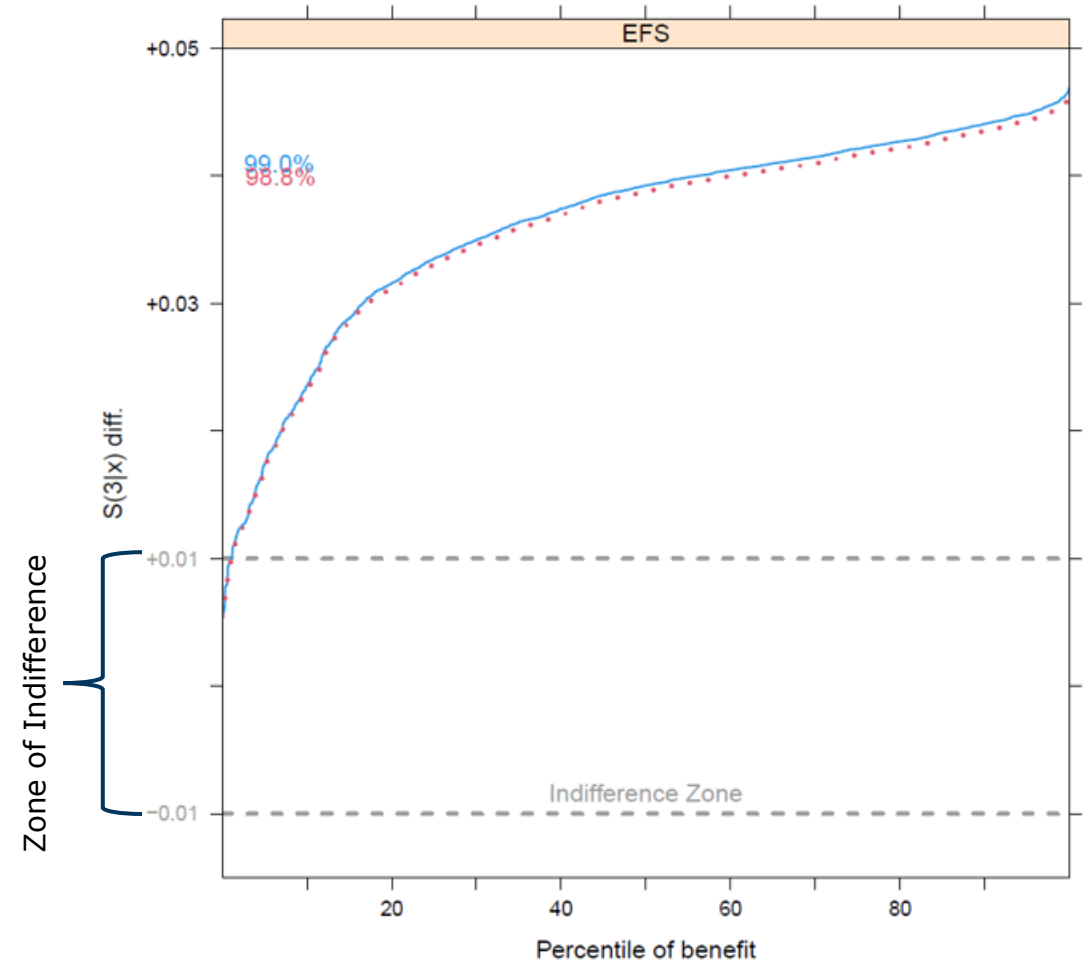
Impact of Donor Sex on OS

- Waterfall plots of OS and differentials based on predictions for the validation set.
- Differentials for a male donor vs. a female; recipient male (female) with a solid blue line (dotted red line).
- Donor sex impact falls within the Zone of Indifference for OS



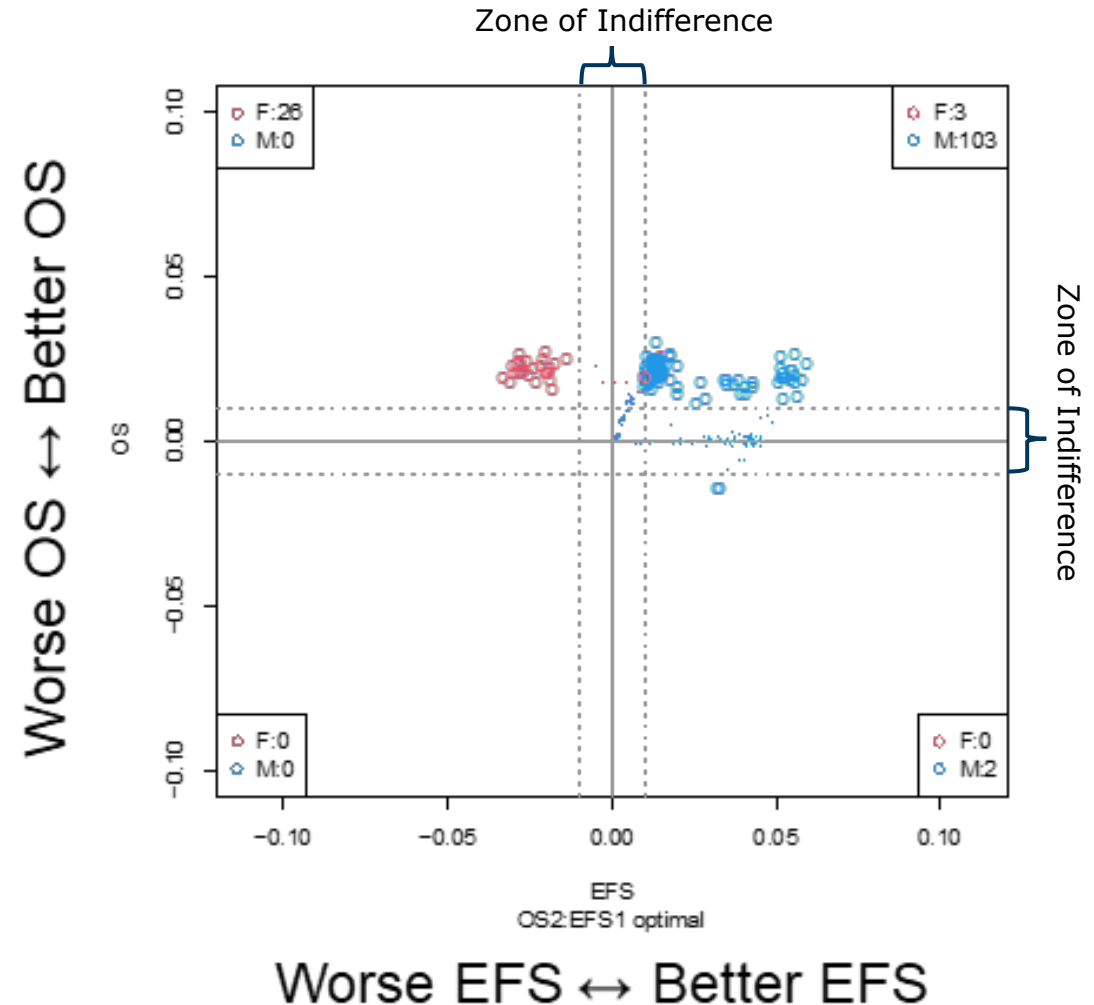
Impact of Donor Sex on EFS

- Waterfall plots of EFS and differentials based on predictions for the validation set.
- Differentials for a male donor vs. a female donor in male (blue solid line) or female (red dotted line) recipients
- Male donors associated with improved EFS for both male (blue) and female (red) recipients



Impact of Donor Sex – OS2:EFS1

- Trade-offs between predicted OS and EFS differentials for the OS2:EFS1 optimal vs. the actual donor in the search archive cohort.
- The y-axis (x-axis) shows OS (EFS) differentials with a zone of indifference (dashed gray lines). The **red** circles (dots) are the optimal youngest **female** donors outside (inside) the zone of indifference. The **blue** circles (dots) are the optimal youngest **male** donors.
- In each corner, we have summarized the circles by sex.
- The upper right corner has the most beneficial choice of donor: both an increase of OS with an increase of EFS. And above the zone of indifference, the upper right is dominated by **male** donors: 103 vs. 3 **females**.



Conclusions

- Using our novel NFT-BART methodology, we show that donor selection to optimize HCT outcomes can be improved by considering both OS and EFS together via weighting 2:1
- This weighted optimization strategy balances outcomes, prioritizing OS while also allowing for consideration of EFS when OS is similar between potential donors.
- Results support previous research showing that choosing among **donors from 18 to 30** results in a negligible improvement of outcomes allowing for flexibility in donor selection.

Acknowledgements

- CIBMTR Statistical Staff
- NMDP Bioinformatics and search strategy groups
- Funding sources:
 - NIH (NCI/NHLBI/NIAID)
 - Office of Naval Research
 - HRSA
- Patients who gave informed consent for CIBMTR research