Supplementary File

Conditioning regimens are associated with distinct patterns of microbiota injury in allogeneic hematopoietic cell transplantation

Contents

Supplementary Methods

Versions of tools

MaAslin2 was modified to output model fit objects and to include interaction terms; the version of the tool used for this analysis can be found at https://github.com/nickp60/Maaslin2 commit `6382ad6`. Ancom2 version 2.1 was used. Other tools and R packages used in this analysis are shown below:

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Running under: macOS Big Sur 10.16

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Supplementary Tables

Table S1. Population characteristics by conditioning regimen

		Bu4/Mel/Flu	Flu/Mel	Flu/Cy/Tt/TBI400	TBI1375/Tt/Cy	Flu/Bu4	Flu/Cy/TBI200	Mel/T/Flu	Clo/Tt/Mel
n		359	233	190	130	87	107	42	40
Sex (%)	Male	215 (59.9)	148 (63.5)	106 (55.8)	66 (50.8)	52 (59.8)	77 (72.0)	27 (64.3)	24 (60.0)
	Female	144 (40.1)	85 (36.5)	84 (44.2)	64 (49.2)	35 (40.2)	30 (28.0)	15 (35.7)	16 (40.0)
Age (median [IQR])		60 [52, 65]	62 [53, 68]	50 [40, 56]	41 [32, 50]	64 [56, 68]	58 [51, 66]	62 [51, 66]	53 [44, 61]
Disease (%)	AML	125 (34.8)	79 (33.9)	82 (43.2)	62 (47.7)	47 (54.0)	0 (0.0)	9 (21.4)	14 (35.0)
	MDS/MPN	128 (35.7)	61 (26.2)	16 (8.4)	20 (15.4)	35 (40.2)	0 (0.0)	23 (54.8)	3 (7.5)
	Lymphoma/CLL	0 (0.0)	57 (24.5)	56 (29.5)	9 (6.9)	0 (0.0)	100 (93.5)	9 (21.4)	0 (0.0)
	ALL	1 (0.3)	20 (8.6)	28 (14.7)	36 (27.7)	4 (4.6)	2 (1.9)	0 (0.0)	19 (47.5)
	Plasma cell neoplasm	99 (27.6)	11 (4.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.4)	0 (0.0)
	Other leukemias	1 (0.3)	4 (1.7)	6 (3.2)	3 (2.3)	1 (1.1)	3 (2.8)	0 (0.0)	4 (10.0)
	Non-malignant disorders	5 (1.4)	1 (0.4)	2 (1.1)	0 (0.0)	0 (0.0)	2 (1.9)	0 (0.0)	0 (0.0)
Previous Allo-HCT (%)	1st allo-HCT	354 (98.6)	212 (91.0)	187 (98.4)	130 (100.0)	82 (94.3)	107 (100.0)	39 (92.9)	30 (75.0)
	2nd allo-HCT	5 (1.4)	21 (9.0)	3 (1.6)	0 (0.0)	5 (5.7)	0 (0.0)	3 (7.1)	10 (25.0)
HCT-CI (median [IQR])		2 [1, 4]	4 [2, 5]	2 [1, 3]	2 [1, 3]	3 [2, 4]	2 [0, 3]	3 [1, 5]	3 [2, 4]
HCT year (median [IQR])		2014 [2012, 2016]	2016 [2014, 2017]	2015 [2013, 2016]	2014 [2012, 2016]	2016 [2015, 2017]	2013 [2011, 2017]	2017 [2017, 2018]	2012 [2011, 2017]
Donor type (%)	Matched unrelated	185 (51.5)	144 (61.8)	21 (11.1)	57 (43.8)	53 (60.9)	51 (47.7)	1 (2.4)	22 (55.0)

	Matched related	102 (28.4)	59 (25.3)	12 (6.3)	63 (48.5)	27 (31.0)	36 (33.6)	0 (0.0)	8 (20.0)
	Cord blood	0 (0.0)	3 (1.3)	156 (82.1)	1 (0.8)	0 (0.0)	11 (10.3)	1 (2.4)	2 (5.0)
	Mismatched non-haploidentical	72 (20.1)	21 (9.0)	1 (0.5)	9 (6.9)	6 (6.9)	9 (8.4)	2 (4.8)	8 (20.0)
	Haploidentical	0 (0.0)	6 (2.6)	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)	38 (90.5)	0 (0.0)
Graft source (%)	PBSC T-cell depleted	359 (100.0)	0 (0.0)	0 (0.0)	117 (90.0)	0 (0.0)	0 (0.0)	0 (0.0)	22 (55.0)
	PBSC unmodified	0 (0.0)	199 (85.4)	34 (17.9)	10 (7.7)	63 (72.4)	94 (87.9)	15 (35.7)	13 (32.5)
	Cord blood	0 (0.0)	3 (1.3)	156 (82.1)	1 (0.8)	0 (0.0)	11 (10.3)	1 (2.4)	2 (5.0)
	BM unmodified	0 (0.0)	31 (13.3)	0 (0.0)	2 (1.5)	24 (27.6)	2 (1.9)	26 (61.9)	3 (7.5)
Conditioning intensity (%)	Ablative	359 (100.0)	0 (0.0)	190 (100.0)	130 (100.0)	87 (100.0)	0 (0.0)	0 (0.0)	40 (100.0)
	Reduced Intensity	0 (0.0)	233 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	42 (100.0)	0 (0.0)
	Nonmyeloablative	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	107 (100.0)	0 (0.0)	0 (0.0)
GVHD prophylaxis (%)	none	359 (100.0)	0 (0.0)	0 (0.0)	117 (90.0)	0 (0.0)	0 (0.0)	0 (0.0)	22 (55.0)
	MTX-based	0 (0.0)	188 (80.7)	35 (18.4)	12 (9.2)	79 (90.8)	95 (88.8)	1 (2.4)	16 (40.0)
	MMF-based	0 (0.0)	14 (6.0)	155 (81.6)	1 (0.8)	1 (1.1)	12 (11.2)	1 (2.4)	2 (5.0)
	PTCy-based	0 (0.0)	31 (13.3)	0 (0.0)	0 (0.0)	7 (8.0)	0 (0.0)	40 (95.2)	0 (0.0)
Exposure to antibiotics* up to day 21 (%)	Exposed	286 (79.7)	117 (50.2)	139 (73.2)	107 (82.3)	41 (47.1)	56 (52.3)	31 (73.8)	27 (67.5)
	Not exposed	73 (20.3)	116 (49.8)	51 (26.8)	23 (17.7)	46 (52.9)	51 (47.7)	11 (26.2)	13 (32.5)

* The frequency of antibiotic exposure considered any exposure to drugs commonly used in this cohort of treatment of neutropenic fever or for *C. difficile* diarrhea (oral vancomycin, imipenem-cilastatin, meropenem, piperacillin-tazobactam, clindamycin, and metronidazole) between the first days of conditioning and days 21 post-allo-HCT.

IQR - interquartile range; AML – acute myeloid leukemia; MDS – myelodysplastic syndrome; MPN – myeloproliferative neoplasm; CLL – chronic lymphocytic leukemia; ALL – acute lymphoblastic leukemia; Allo-HCT – allogeneic hematopoietic cell transplantation; HCT-CI - hematopoietic cell transplantation-specific comorbidity index; MTX – methotrexate; MMF – mycophenolate mofetil; PTCy – post-transplantation cyclophosphamide.

Table S2. Greater conditioning intensity is associated with reduction in log diversity in a Generalized Estimating Equations multivariable model

Characteristic	Beta	95% CI	p-value
Days from allo-HCT to sample collection*s			
Spline (level 1)	-1.4	-1.9, -0.82	<0.001
Spline (level 2)	-3.3	-3.6, -3.0	<0.001
Spline (level 3)	-1.6	-2.0, -1.2	<0.001
Conditioning intensity			
Ablative	—	—	
Non-ablative	0.42	0.31, 0.53	<0.001
Reduced Intensity	0.15	0.07, 0.22	<0.001
Age	0	0.00, 0.01	<0.001
Sex			
Female	—	—	
Male	0.05	-0.01, 0.11	0.074
Sample exposed to GVHD prophylaxis			
Not-exposed	—	—	
Exposed	-0.1	-0.18, -0.03	0.007
Sample exposed to non-prophylactic antibiotics			
Not-exposed			
Exposed	-0.25	-0.31, -0.19	<0.001
Sample exposed to conditioning			
Not-exposed			
Exposed	0.04	-0.03, 0.12	0.3

* The timeframe considered was from day -20 to day +30 relative to allo-HCT.

Allo-HCT – allogeneic hematopoietic cell transplantation; GVHD – graft-versus-host disease

Table S3. A multivariable Generalized Estimating Equations model to evaluate the association between log diversity and conditioning intensity in an external multicenter cohort

Characteristic	Beta	95% CI	p-value
Days from allo-HCT to sample collection*s			
Spline (level 1)	-0.78	-1.5, -0.09	0.026
Spline (level 2)	-0.55	-1.2, 0.07	0.084
Spline (level 3)	-0.38	-0.88, 0.11	0.13
Conditioning intensity			
Ablative	—	—	
Non-ablative	0.45	0.15, 0.77	0.005
Reduced Intensity	0.06	-0.17, 0.26	0.6
Age	-0.01	-0.01, 0.00	0.13
Sex			
Female	—	—	
Male	-0.02	-0.21, 0.16	0.8

Table S4. Conditioning regimens are associated with a differential reduction in log diversity in a Generalized Estimating Equations multivariable model

Characteristic	Beta	95% CI	p-value
Days from allo-HCT to sample collection*			
Spline (level 1)	-1.4	-1.9, -0.83	<0.001
Spline (level 2)	-3.3	-3.6, -3.1	<0.001
Spline (level 3)	-1.6	-2.0, -1.2	<0.001
Conditioning intensity			
TBI1375/Tt/Cy	—	—	
Bu4/Mel/Flu	0.08	-0.03, 0.19	0.2
Clo/Tt/Mel	-0.11	-0.27, 0.06	0.2
Flu/Bu4	0.23	0.09, 0.38	0.001
Flu/Cy/TBI200	0.52	0.38, 0.66	<0.001
Flu/Cy/Tt/TBI400	0.09	-0.03, 0.20	0.14
Flu/Mel	0.25	0.13, 0.37	<0.001
Mel/Tt/Flu	0.22	0.05, 0.40	0.01
Age	0	0.00, 0.01	<0.001
Sex			
Female	—	—	
Male	0.05	-0.01, 0.11	0.076
Sample exposed to GVHD prophylaxis			
Not-exposed	—	—	
Exposed	-0.1	-0.17, -0.03	0.008
Sample exposed to non-prophylactic antibiotic			
Not-exposed			
Exposed	-0.25	-0.31, -0.19	<0.001
Sample exposed to conditioning			
Not-exposed			
Exposed	0.04	-0.04, 0.12	0.3

* The timeframe considered was from day -20 to day +30 relative to allo-HCT.

Allo-HCT – allogeneic hematopoietic cell transplantation; GVHD – graft-versus-host disease

Figures Captions

Figure S1. Key population characteristics vary between conditioning regimens. Recipients of different conditioning regimens were enriched for transplant characteristics with respect to disease, graft source, GVHD prophylaxis, and frequency of exposure to antibiotics (right panel). For example, cord-blood recipients typically received Flu/Cy/Tt10/TBI400 and mycophenolate mofetil-based GVHD prophylaxis. For example, the Bu4/Mel/Flu regimen was almost exclusively administered with peripheral blood CD34-selected grafts without additional GVHD prophylaxis. The frequency of antibiotic exposure considered any exposure to drugs commonly used in this cohort of treatment of neutropenic fever or for *C. difficile* diarrhea (oral vancomycin, imipenem-cilastatin, meropenem, piperacillin-tazobactam, clindamycin, and metronidazole) between the first days of conditioning and days 21 post-allo-HCT.

AML – acute myeloid leukemial; CLL – chronic lymphocytic leukemia; MDS – myelodysplastic syndrome; ALL – acute lymphoblastic leukemia; MAC – myeloablative conditioning; RIC – reduced-intensity conditioning; NMA – nonmyeloablative conditioning; GVHD – graft-versus-host disease ; PB – peripheral blood; BM – bone marrow; MTX – methotrexate; MMF – mycophenolate mofetil; PTCy – post-transplantation cyclophosphamide

Figure S2. Distribution and α-diversity of stool sample over time from allogeneic hematopoietic cell transplantation. Intestinal microbiota diversity, as measured by 16S sequencing and the inverse Simpson index, declines over time. A mean of 6.5 and 4.3 samples per patient were collected between days -20 to 30 and -10 to 10, respectively.

HCT – hematopoietic cell transplantation

Figure S3. Incidence of bacterial monodomination over time. Monodomination is defined as a relative-abundance threshold of any single ASV of at least 30%.(1)

HCT – hematopoietic cell transplantation

Figure S4. Different modeling techniques demonstrate changes in similar taxa. The bivariate analysis considering the effect of time and conditioning regimen (with random effects to account for repeated measures) was performed with several different differential abundance tools.(2-7) While there were fewer significant hits detected by Ancom, overall there was strong

agreement between the tools despite the different underlying statistical approaches used by each.

Figure S5. Multivariate analysis of taxonomic responses to conditioning. (A) MaAsLin2 model adjusting for time of sampling, conditioning regimens, antibiotic exposures, underlying disease, GVHD prophylaxis, and clinical features reveals a differential association between microbial taxa and conditioning regimens; samples were limited to those collected between day 0 and 12 post-transplant. Antibiotic exposure was encoded as the number of days between day -30 relative to transplant and sample collection when the patient received an antibiotic of the class. Notably, the microbial landscape is also strongly shaped by antibiotic exposures. In this analysis, the baseline for the conditioning exposures was set to the first sample on or after day 0. The strong associations with the aggregated "any" exposure to GVHD prophylaxis drugs prompted the following panel **Figure S5B** in which the GVHD prophylaxis drug exposures were encoded individually as pre/post exposure, per sample. **Figure S5C** shows the effects of both the antibiotic and the individual conditioning drug exposures in the conditioning window (day -10 to 0 relative to transplant). Conditioning regimen was encoded as the proportion of the drug course received at the time of sampling. This highlights the changes attributable to the conditioning individual drugs, with the caveat that there is a strong correlation structure among the drugs (i.e., the conditioning regimens).

GVHD – graft-versus-host disease; PPX – prophylaxis; ALL – acute lymphoblastic leukemia; AML – acute myeloid leukemia; CLL – chronic lymphocytic leukemia; MDS – myelodysplastic syndrome; MPN – myeloproliferative neoplasm; PBSC – peripheral blood stem cell; drt – time from allogeneic hematopoietic cell transplantation

Figure S6. Correlation matrix between patient, disease, and transplantation features. Categorical data were one-hot recoded, and Pearson correlations were calculated. Purple indicates a negative correlation, green indicates a positive correlation; circles are drawn around significant associations (Benjamini Hochberg corrected $p < .01$). Prefixes proph, abx, and cond refer to GVHD prophylaxis, antibiotic, and conditioning drugs, respectively.

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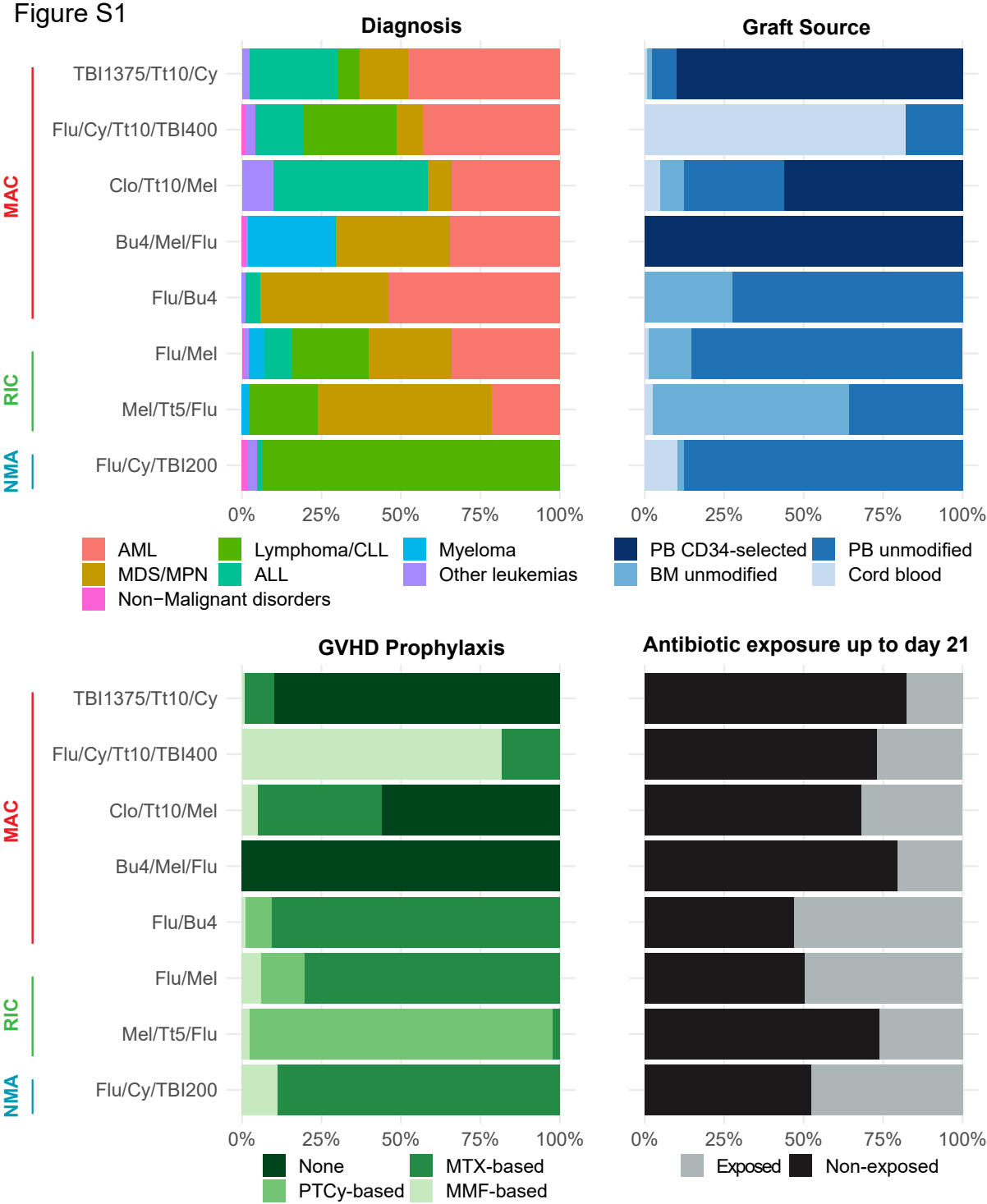
1. Taur Y, Xavier JB, Lipuma L, Ubeda C, Goldberg J, Gobourne A*, et al.* Intestinal domination and the risk of bacteremia in patients undergoing allogeneic hematopoietic stem cell transplantation. Clinical infectious diseases **2012**;55(7):905-14.
2. Martin BD, Witten D, Willis AD. Modeling microbial abundances and dysbiosis with beta-binomial regression. The annals of applied statistics **2020**;14(1):94.
3. Kaul A, Mandal S, Davidov O, Peddada SD. Analysis of microbiome data in the presence of excess zeros. Frontiers in microbiology **2017**;8:2114.
4. Lin H, Peddada SD. Analysis of compositions of microbiomes with bias correction. Nature communications **2020**;11(1):3514 doi 10.1038/s41467-020-17041-7.
5. Paulson JN, Stine OC, Bravo HC, Pop M. Differential abundance analysis for microbial marker-gene surveys. Nature methods **2013**;10(12):1200-2.
6. Paulson JN, Talukder H, Bravo HC. Longitudinal differential abundance analysis of microbial marker-gene surveys using smoothing splines. BioRxiv **2017**:099457.
7. Paulson JN, Pop M, Bravo HC. metagenomeSeq: Statistical analysis for sparse high-throughput sequencing. Bioconductor package **2013**(0):191.

Figure S1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Bu4/Mel/Flu
Flu/Bu4
Flu/Mel
Mel/Tt5/Flu
Flu/Cy/TBI200
MAC
RIC
NMA
0%
25%
50%
75%
100%
AML
MDS/MPN
Non−Malignant disorders
Lymphoma/CLL
ALL
Myeloma
Other leukemias
PB CD34-selected
BM unmodified
PB unmodified
Cord blood
GVHD Prophylaxis
Antibiotic exposure up to day 21
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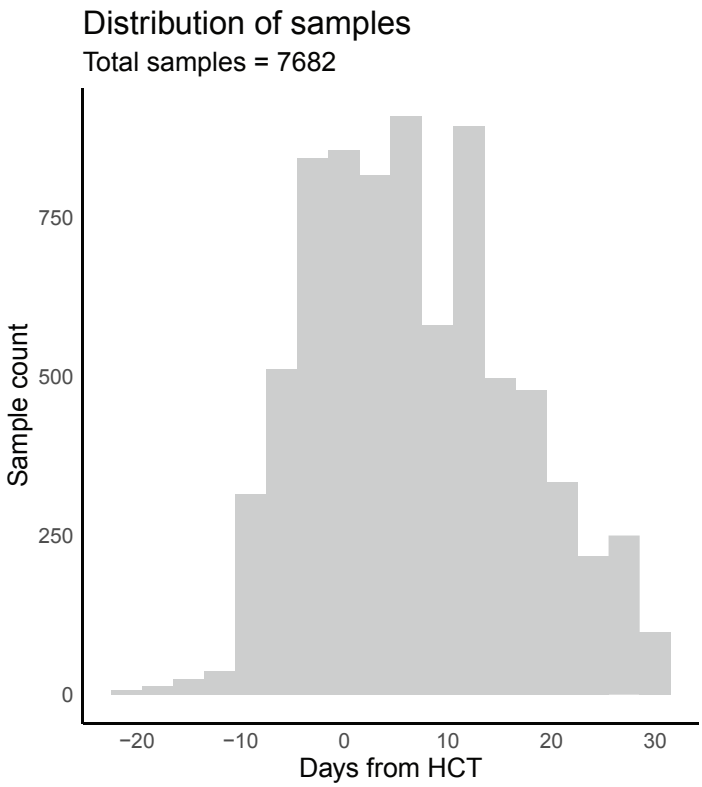
PTCy-based
MTX-based
MMF-based
Exposed
Non-exposed

Figure S2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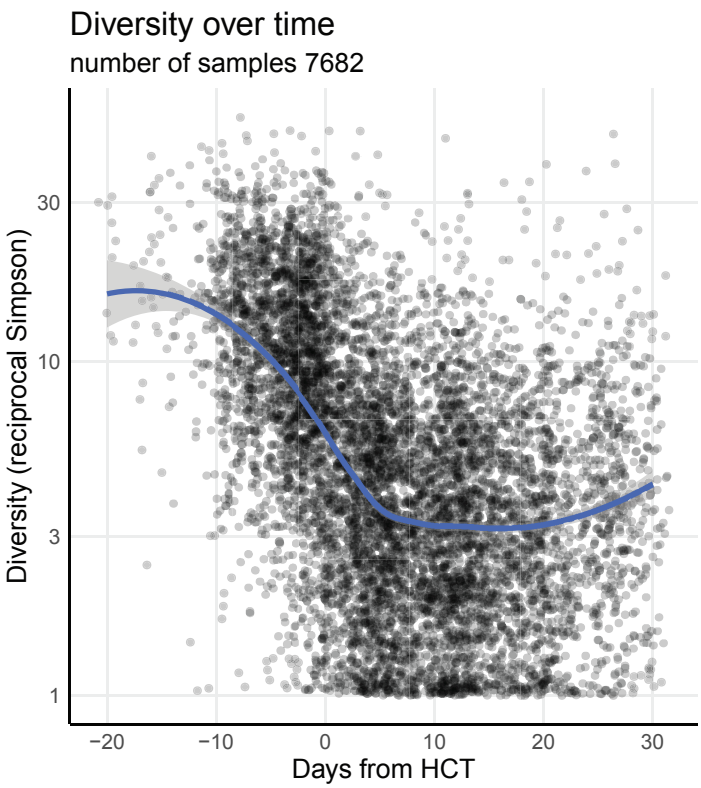
−20
−10
0
10
20
30
Days from HCT


Diversity over time
number of samples 7682
Diversity (reciprocal Simpson)
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10
3
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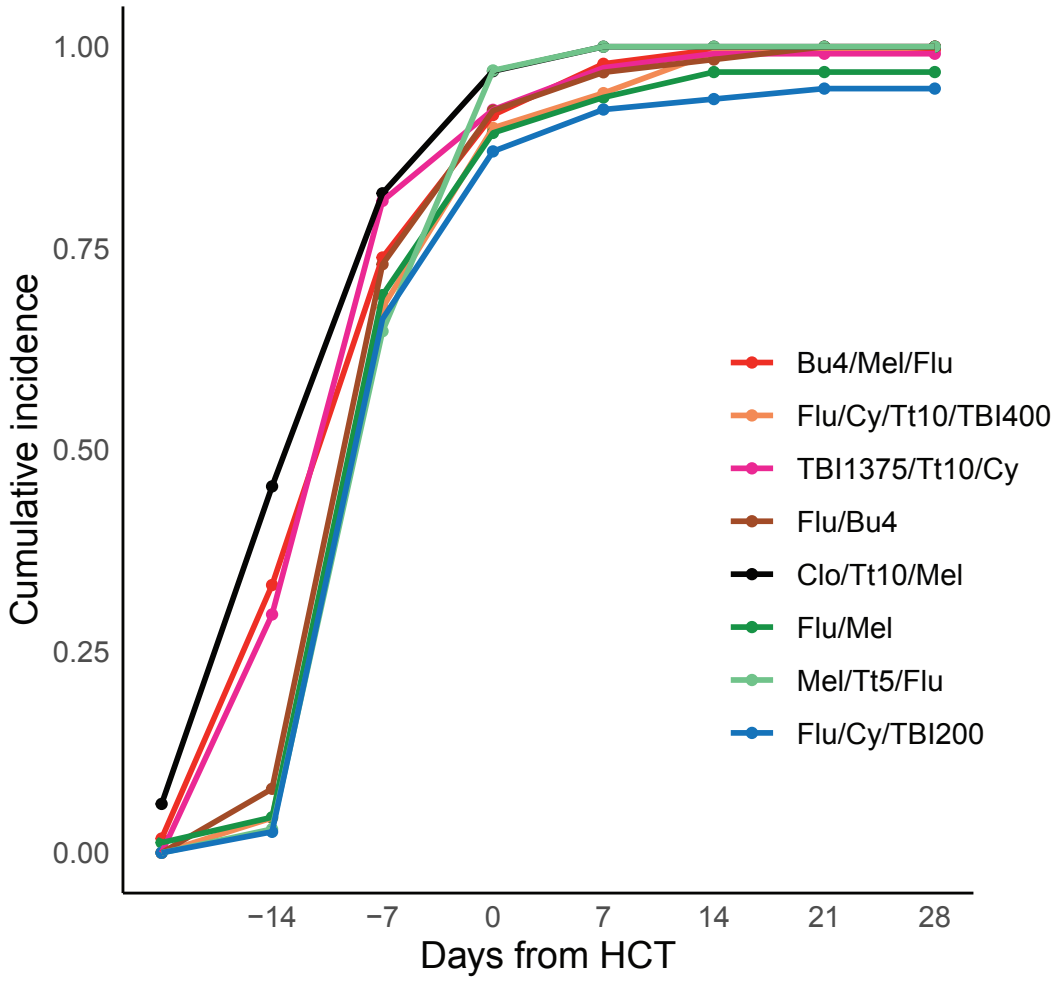
−20
−10
0
10
20
30
Days from HCT

Figure S3


1.00
0.75
0.50
0.25
0.00
Cumulative incidence
−14
−7
0
7
14
21
28
Days from HCT
Bu4/Mel/Flu
Flu/Cy/Tt10/TBI400
TBI1375/Tt10/Cy
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Clo/Tt10/Mel
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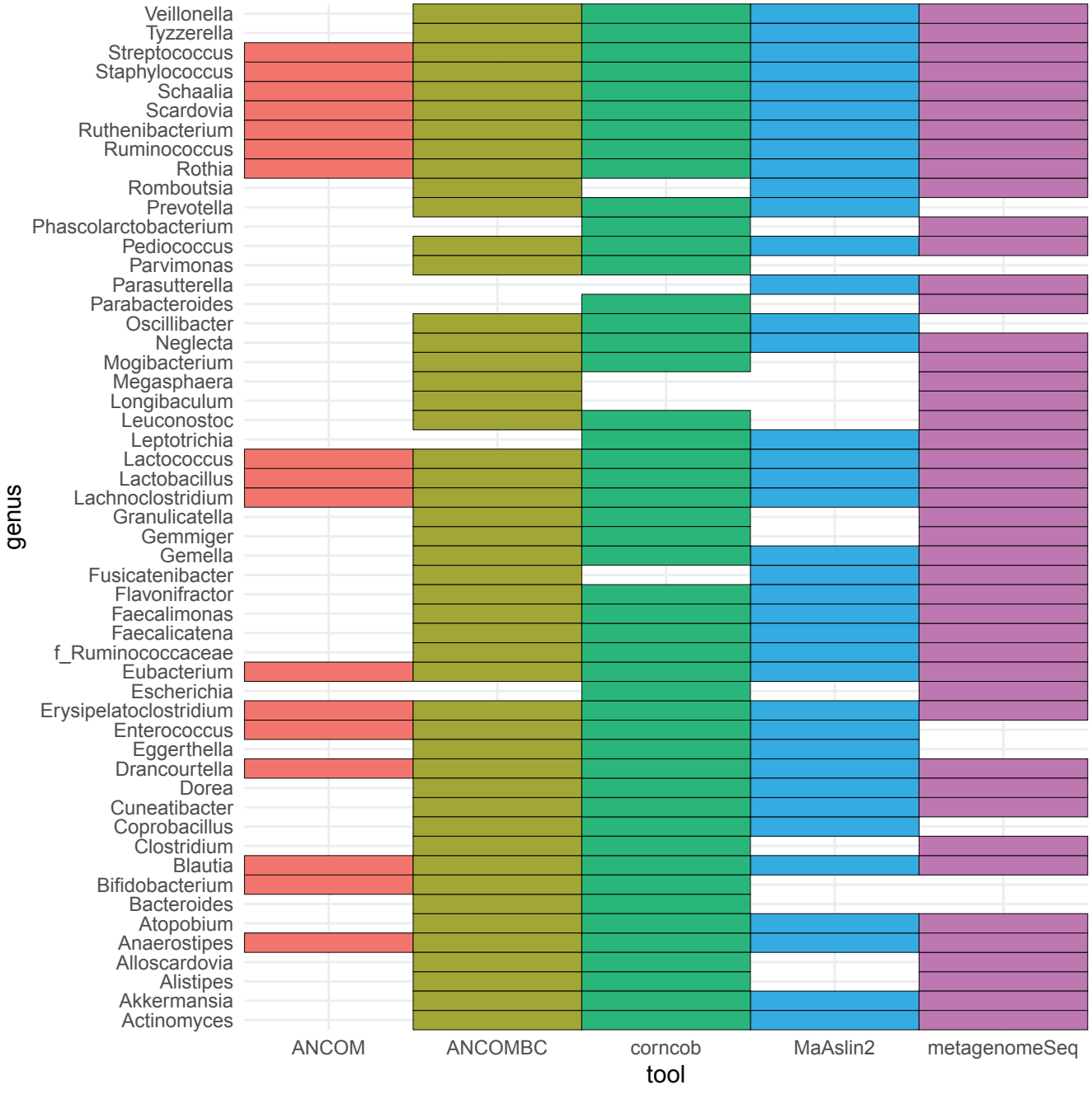
Flu/Cy/TBI200

Figure S4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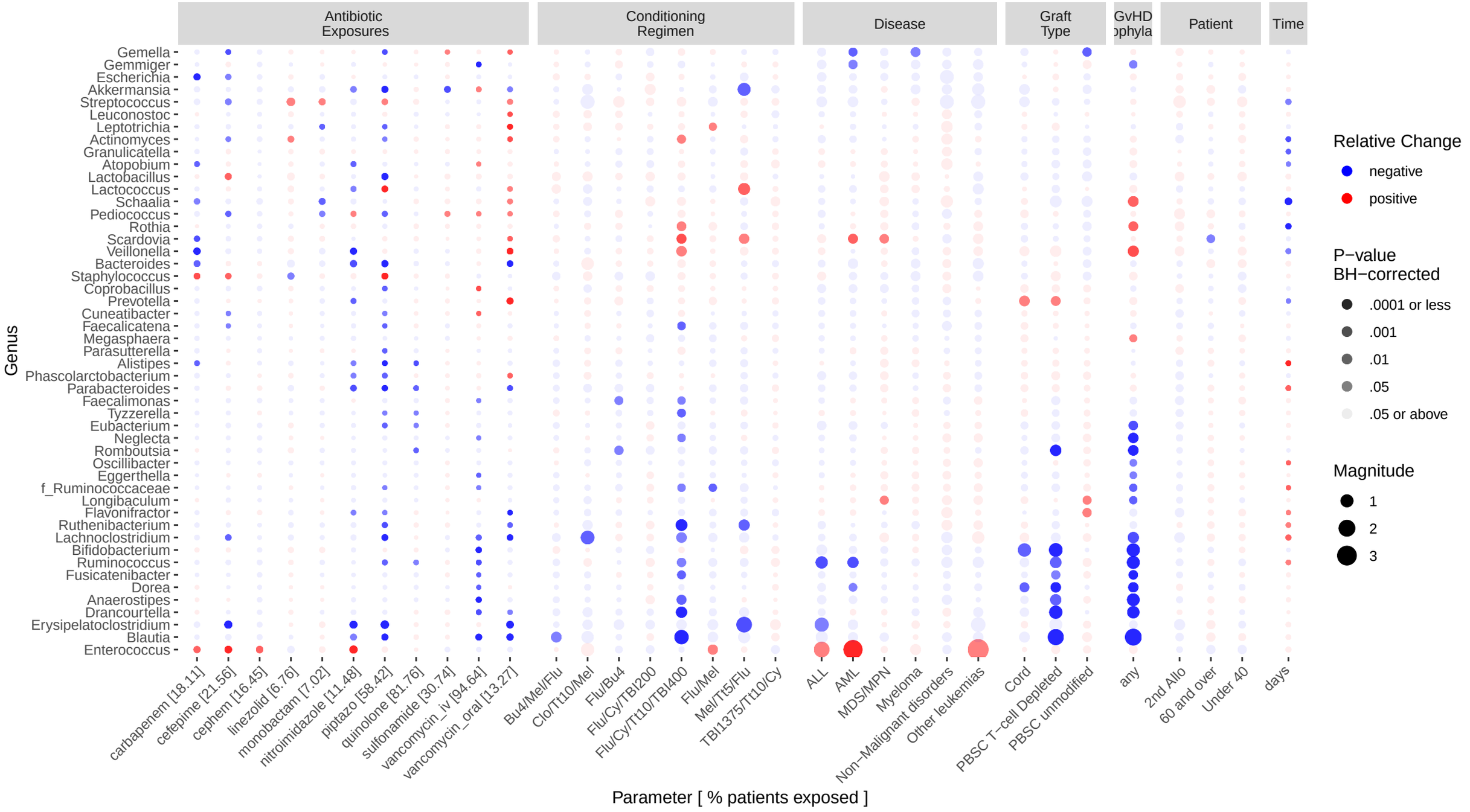
Lactococcus
Lactobacillus
Lachnoclostridium
Granulicatella
Gemmiger
Gemella
Fusicatenibacter
Flavonifractor
Faecalimonas
Faecalicatena
f_Ruminococcaceae
Eubacterium
Escherichia
Erysipelatoclostridium
Enterococcus
Eggerthella
Drancourtella
Dorea
Cuneatibacter
Coprobacillus
Clostridium
Blautia
Bifidobacterium
Bacteroides
Atopobium
Anaerostipes
Alloscardovia
Alistipes
Akkermansia
Actinomyces
genus
ANCOM
ANCOMBC
corncob
MaAslin2
metagenomeSeq
tool

Figure S5A

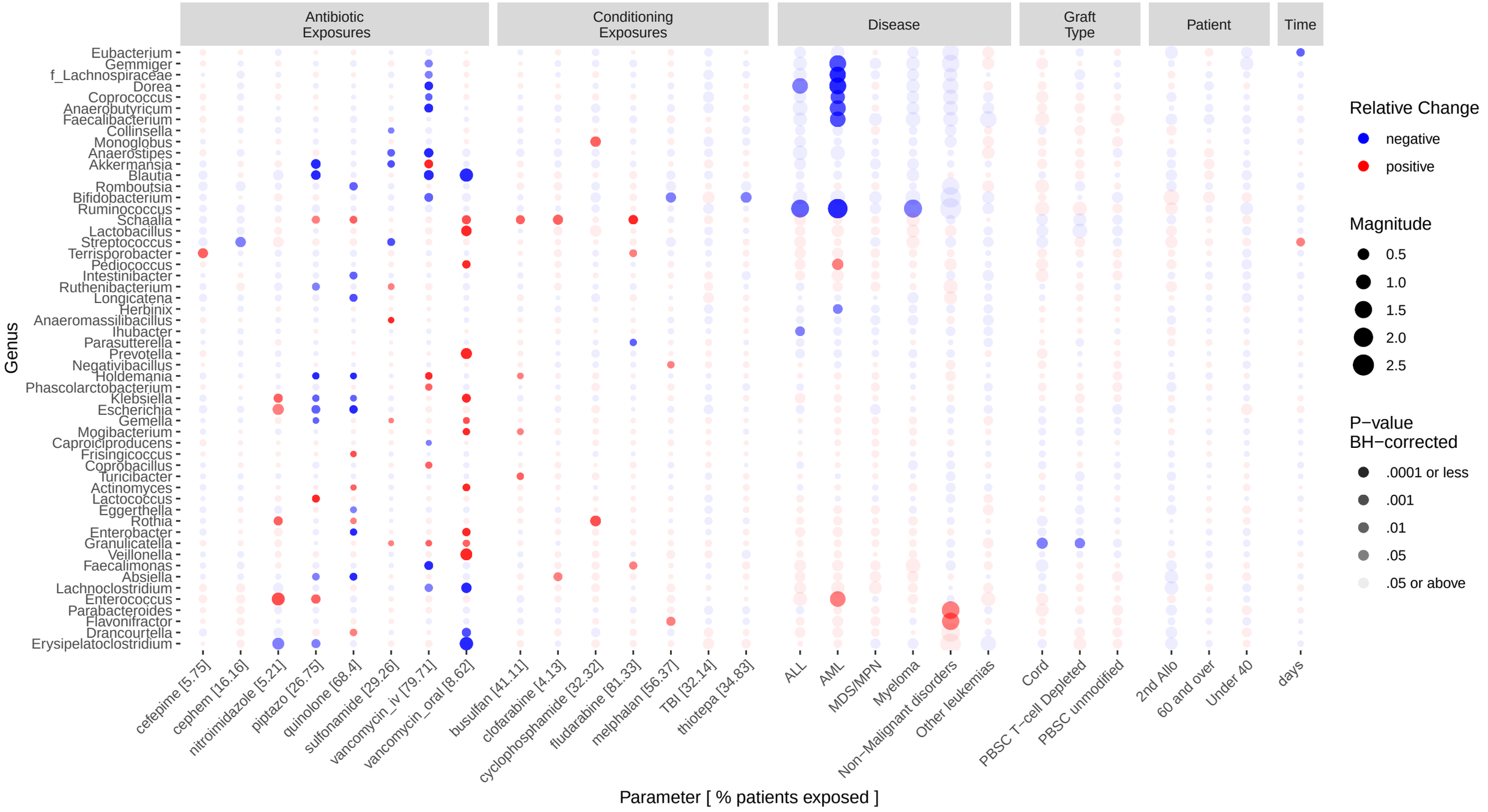
784 patient transplants, 3390 samples
Excluded Antibiotic classes: abx_aminoglycoside [2.55], abx_antiparasitic [1.15], abx_lincosamides [1.02], abx_lipopeptide [1.66], abx_macrolide [3.06], abx_penicillins [2.55], abx_tetracycline [0.89]



Disease is relative to Lymphoma/CLL;
Age is relative to 40−60 bracket, graft type is relative to BM.

Figure S5B

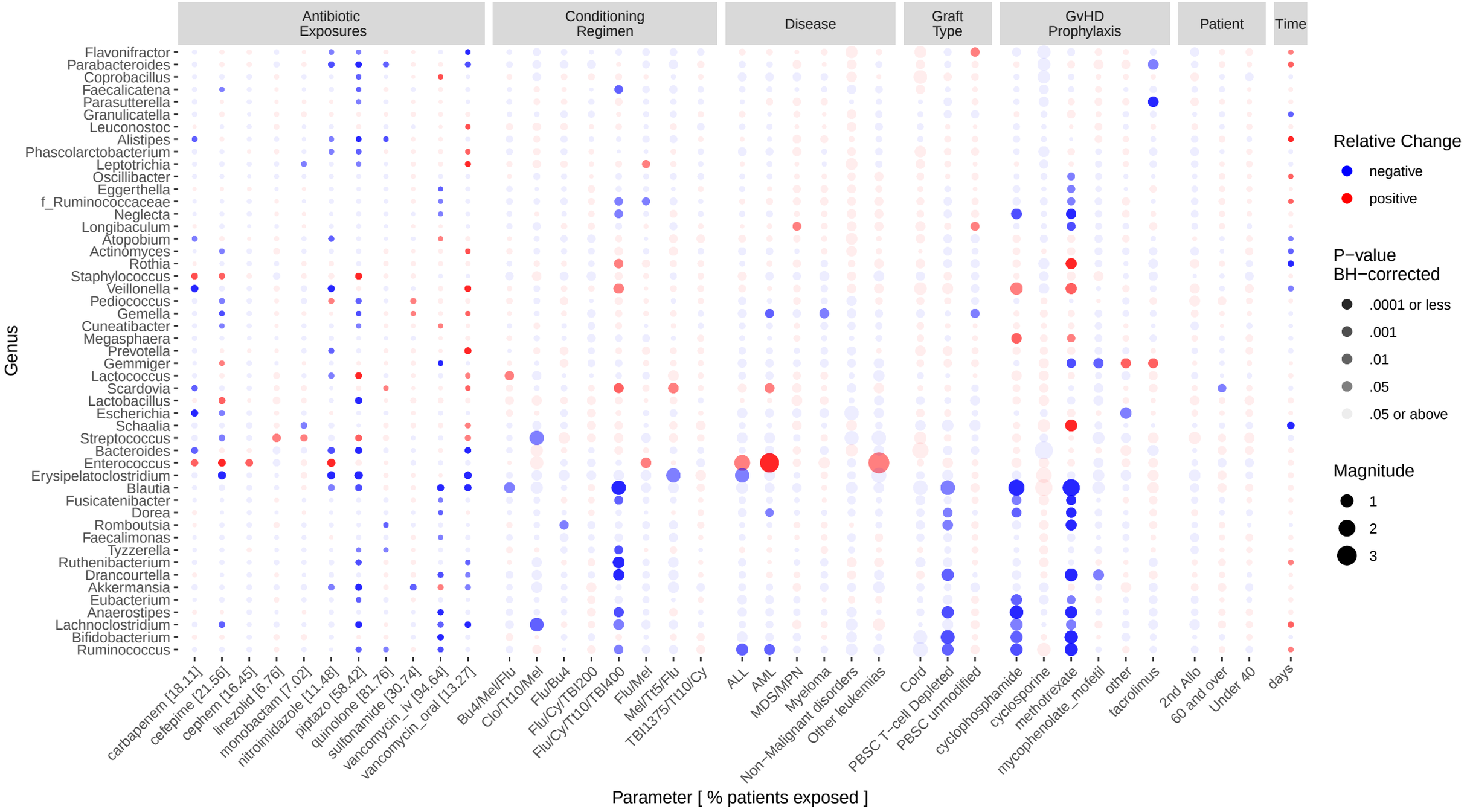
557 patient transplants, 1588 samples
Excluded Antibiotic classes: abx_aminoglycoside [0.36], abx_antiparasitic [1.26], abx_carbapenem [1.44],
abx_cefepime [4.13], abx_lincosamides [0.54], abx_lipopeptide [0.54], abx_macrolide [1.97], abx_monobactam [1.8], abx_nitroimidazole [3.41],
abx_oxazolidone [0.36], abx_penicillins [1.44], abx_tetracycline [0.18]



Disease is relative to Lymphoma/CLL;
Age is relative to 40−60 bracket, graft type is relative to BM.

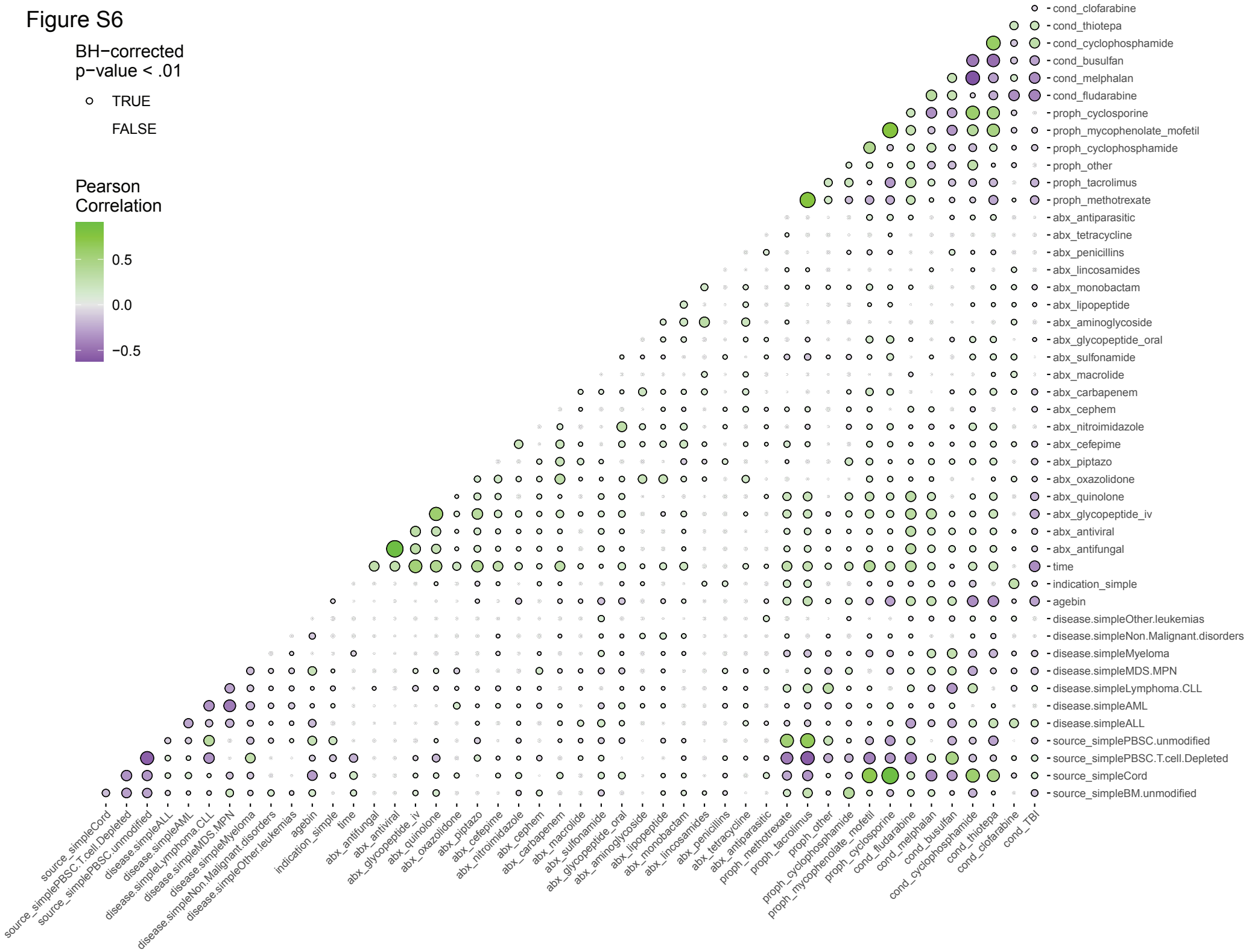
Figure S5C

784 patient transplants, 3390 samples
Excluded Antibiotic classes: abx_aminoglycoside [2.55], abx_antiparasitic [1.15], abx_lincosamides [1.02], abx_lipopeptide [1.66], abx_macrolide [3.06], abx_penicillins [2.55], abx_tetracycline [0.89]



Disease is relative to Lymphoma/CLL;
Age is relative to 40−60 bracket, graft type is relative to BM.

Figure S6


BH−corrected
p−value < .01
TRUE
FALSE
Pearson
Correlation
0.5
0.0
−0.5
cond_clofarabine
cond_thiotepa
cond_cyclophosphamide
cond_busulfan
cond_melphalan
cond_fludarabine
proph_cyclosporine
proph_mycophenolate_mofetil
proph_cyclophosphamide
proph_other
proph_tacrolimus
proph_methotrexate
abx_antiparasitic
abx_tetracycline
abx_penicillins
abx_lincosamides
abx_monobactam
abx_lipopeptide
abx_aminoglycoside
abx_glycopeptide_oral
abx_sulfonamide
abx_macrolide
abx_carbapenem
abx_cephem
abx_nitroimidazole
abx_cefepime
abx_piptazo
abx_oxazolidone
abx_quinolone
abx_glycopeptide_iv
abx_antiviral
abx_antifungal
time
indication_simple
agebin
disease.simpleOther.leukemias
disease.simpleNon.Malignant.disorders
disease.simpleMyeloma
disease.simpleMDS.MPN
disease.simpleLymphoma.CLL
disease.simpleAML
disease.simpleALL
source_simplePBSC.unmodified
source_simplePBSC.T.cell.Depleted
source_simpleCord
source_simpleBM.unmodified
source_simpleCord
source_simplePBSC.T.cell.Depleted
source_simplePBSC.unmodified
disease.simpleALL
disease.simpleAML
disease.simpleLymphoma.CLL
disease.simpleMDS.MPN
disease.simpleMyeloma
disease.simpleNon.Malignant.disorders
disease.simpleOther.leukemias
agebin
indication_simple
time
abx_antifungal
abx_antiviral
abx_glycopeptide_iv
abx_quinolone
abx_oxazolidone
abx_piptazo
abx_cefepime
abx_nitroimidazole
abx_cephem
abx_carbapenem
abx_macrolide
abx_sulfonamide
abx_glycopeptide_oral
abx_aminoglycoside
abx_lipopeptide
abx_monobactam
abx_lincosamides
abx_penicillins
abx_tetracycline
abx_antiparasitic
proph_methotrexate
proph_tacrolimus
proph_other
proph_cyclophosphamide
proph_mycophenolate_mofetil
proph_cyclosporine
cond_fludarabine
cond_melphalan
cond_busulfan
cond_cyclophosphamide
cond_thiotepa
cond_clofarabine
cond_TBI