

Table S1. List of abbreviations

Abbreviation	Definition
AA	archetypal analysis
ABMR	antibody-mediated rejection
AMATs	alternative macrophage activation transcripts
ATAGC	Alberta Transplant Applied Genomics Centre
AUC	area under the curve
BAT	B cell-associated transcripts
CAV	cardiac allograft vasculopathy
clRIT	cardiac injury and repair transcripts
DAMP	damage-associated molecular pattern transcripts
DSA	Donor-specific antibody
DSAST	DSA-selective transcripts
EABMR	Early-stage ABMR
EMB	endomyocardial biopsy
FABMR	Fully-developed ABMR
gmlnet	a package that fits a generalized linear model via penalized maximum likelihood
GRIT	Gamma interferon and rejection induced transcripts
HT	heart parenchymal transcripts
HT1	heart parenchymal transcripts set 1
HT2	heart parenchymal transcripts set 2
IGT	immunoglobulin transcripts
INTERHEART	Diagnostic and Therapeutic Applications of Microarrays in Heart Transplantation, a Multicenter Study (ClinicalTrials.gov Identifier: NCT02670408)
Injury archetype	archetypal model for assessing cardiac injury
IRRAT	injury-and-repair transcripts
IRITD3	injury-repair induced transcripts day 3
IRITD5	injury-repair induced transcripts day 5
KCL	Kashi Clinical Laboratories
LVEF	left ventricular ejection fraction
LoLVEF _{Prob}	Low LVEF probability classifier
MMDx	Molecular Microscope [®] Diagnostic System
NKB	natural killer cell burden
NR	No rejection
pABMR	Probable ABMR
PBTs	pathogenesis-based transcript sets
PCA	principal component analysis
PC1	principal component 1
PC2	principal component 2
PC3	principal component 3
pTCMR	Probable TCMR
QCAT	Quantitative cytotoxic T cell-associated transcripts
QCMAT	Quantitative constitutive macrophage-associated transcripts
RATs	rejection-associated transcripts
TCMR	T cell-mediated rejection
TCMR1	TCMR type 1
TCMR2	TCMR type 2
TxBx	Time of biopsy post-transplant
UMAP	Uniform manifold approximation and projection

Table S2. INTERHEART investigators (N=3230, ClinicalTrials.gov #NCT02670408)

Location	Principal Investigator	Number of biopsies
Edmonton, AB, Canada	Daniel Kim	128
Prague, CZ	Vojtech Melenovsky	1
Los Angeles, CA, USA	Jon Kobashigawa & Jignesh Patel	80
Salt Lake City, UT, USA	Josef Stehlik	47
Dallas, TX, USA	Shelley Hall & Aayla Jamil	126
Los Angeles, CA, USA	Mario Deng, Eugene Depasquale, & Martin Cadeiras (currently in Davis, CA, USA)	13
Richmond, VA, USA	Keyur Shah	24
Bologna, Italy	Luciano Potena	384
A Coruña, Spain	Marisa Crespo	276
Vienna, Austria	Andreas Zuckermann, Arezu Aliabadi-Zuckermann, & Johannes Gökler	196
Sydney, Australia	Peter Macdonald	153

Table S3. Biopsy characteristics and patient demographics (N=3230)	
Biopsy characteristics	All biopsies N=3230
Days to biopsy post-transplant (TxBx)	
<i>Mean</i>	1181
<i>Median (range)</i>	350 (1,11007)
Days to most recent follow-up after biopsy	
<i>Mean</i>	610
<i>Median (range)</i>	313 (1,3854)
Indication for biopsy	
<i>Clinical including follow-up (% of known)</i>	259 (18.5)
<i>Protocol/surveillance biopsy (% of known)</i>	1142 (81.5)
<i>Not stated (% of total)</i>	1829 (56.6)
DSA Status	
<i>DSA-positive</i>	653
<i>DSA-negative</i>	877
<i>Not recorded</i>	1700
Patient demographics	All patients N=1091
Mean patient age (range) (at Tx)	49.6 (2, 80)
Age > 65 years (%) (at Tx)	110 (10.1)
Mean donor age (range)	39.8 (6, 71)
Patient sex	
<i>Male (% of known)</i>	700 (66.1)
<i>Female (% of known)</i>	359 (33.9)
<i>Unknown</i>	32 (2171 including the service laboratory biopsies)
Donor sex	
<i>Male (% of known)</i>	521 (65.5)
<i>Female (% of known)</i>	275 (34.5)
<i>Not available (% of total)</i>	296 or 2434
Patient had a previous failed heart transplant	*24/670 with data available (3.6%)
Heart status at last follow-up	
<i>Alive at last follow-up (% of known)</i>	806 (90.6)
<i>Deceased (% of known)</i>	84 (9.4)
<i>Not available (% of total)</i>	202 (18.5)
Primary disease ^A	
<i>Other Cardiomyopathies</i>	509 (65%)
<i>Congenital Heart Defect (% of known)</i>	39 (5%)
<i>Coronary Artery Disease (% of known)</i>	86 (11%)
<i>Other (% of known)</i>	145 (19%)
<i>Not available (% of total)</i>	312

^A Some patients received more than one primary diagnosis

Table S4. Algorithms, AUCs, and available values for the classifiers used to classify rejection in the heart biopsies

Classifier category	Classifier ^A	AUC ^B	Algorithm	Predicting	Training feature
Kidney-derived ABMR-related	ABMR _{Prob}	0.83	ABMR vs everything else with TG/ABMR suspicious excluded	ABMR	histologic ABMR
	ptc>0 _{Prob}	0.83	ptc lesions >0 vs =0	ptc>0	ptc-lesion scores
	g>0 _{Prob}	0.81	g lesions >0 vs =0	g>0	g-lesion scores
Kidney-derived TCMR-related	TCMR _{Prob}	0.82	TCMR vs everything else	TCMR	Histologic TCMR
	t>1 _{Prob}	0.83	t lesions >1 vs ≤1	t>1	t-lesion scores
	i>1 _{Prob}	0.84	i lesions >1 vs ≤1	i>1	i-lesion scores
Kidney-derived All rejection	Rejection _{Prob}	0.85	All rejection (A+T+M) vs everything else	All rejection	histologic rejection
LVEF	LoLVEF _{Prob}	0.73	LVEF≤55 vs. LVEF>55	LVEF≤55	LVEF measurement

^A The 3 ABMR-related and 3 TCMR-related classifiers were used to build the PCA and AA. Biopsies called 'inadequate' by histology were excluded from any classifier development algorithm.
^B Reported as a C statistic.

Table S5. Description of pathogenesis-based transcript sets (PBTs)^A

	Category	Abbreviation	Description
Rejection	Rejection-related	GRIT3	Interferon gamma-inducible (1, 2)
		Rej-RAT	Rejection-associated (3)
	TCMR-related	TCMR-RAT	TCMR-associated (3)
		QCAT	Cytotoxic T cell associated (2, 4)
		TCB	T-cell burden related (3)
	ABMR-related	ABMR-RAT	ABMR-associated (1, 3)
		NKB	NK cell burden (5)
DSAST		DSA selective transcripts (6)	
Injury ^B	Recent injury-related	IRITD3	Injury-repair induced, day 3 (IRITD3) (7)
		IRITD5	Injury-repair induced, day 5 (IRITD3) (7)
		IRRAT30	Injury-repair associated (IRRAT30) (8)
	Late injury (atrophy-fibrosis)-related	IGT	Cardiac injury and repair induced transcripts (9)
	Normal heart transcripts	HT1	Immunoglobulin transcripts (IGT) (10)
		HT2	Normal heart transcripts-set 1 (heart-selective compared with kidneys) (11,12)
	Macrophage-related	AMAT1	Normal heart transcripts-set 2 (heart-selective compared with kidneys) (11,12)
		QCMAT	Alternatively activated macrophage (AMAT1) (13)

^A <https://www.ualberta.ca/medicine/institutes-centres-groups/ataqc/research/gene-lists>.

^B Transcript sets used as input into the injury 5 archetype model.

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Table S6. Complete list of molecular features of the 7 rejection archetype groups in the N=3230 population

Biopsy groups		No rejection	Minor	TCMR1	TCMR2	TCMR/ Mixed	EABMR	FABMR
	N	1564 (48.4%)	777 (24.1%)	75 (2.3%)	88 (2.7%)	88 (2.7%)	127 (3.9%)	511 (16%)
	Days posttransplant (median)	<i>189</i>	356	360	660	938	266	1328
	Days posttransplant (mean)	<i>1012</i>	1157	1077	1183	1497	1116	1708
Macrophages	AMAT1	<i>0.84</i>	0.99	2.22	1.75	1.95	1.45	1.44
	QCMAT	<i>0.78</i>	0.89	2.01	1.54	1.71	1.23	1.21
Atrophy-fibrosis	BAT	<i>0.79</i>	0.84	1.14	1.07	1.05	0.89	0.90
	IGT	<i>0.83</i>	1.05	2.3	2.44	2.42	1.56	1.51
Recent injury	cIRIT	<i>0.84</i>	0.85	1.21	1.06	1.11	0.97	0.97
	DAMP	<i>0.79</i>	0.80	1.01	0.83	0.91	0.89	0.77
	IRITD3	<i>0.83</i>	0.84	0.98	0.91	0.96	0.90	0.92
	IRITD5	<i>0.86</i>	0.89	1.08	0.96	1.03	0.98	1.01
	IRRAT	<i>0.86</i>	0.92	1.41	1.18	1.28	1.16	1.08
De-differentiation	HT1	0.83	0.82	<i>0.44</i>	0.58	0.53	0.72	0.71
	HT2	0.85	0.84	<i>0.23</i>	0.46	0.40	0.69	0.70
ABMR-related	ABMR-RAT	<i>0.76</i>	1.17	2.30	1.79	2.34	1.72	2.04
	NKB	<i>0.89</i>	1.12	1.41	1.04	1.75	1.35	1.91
	DSAST	<i>0.78</i>	0.95	0.92	0.83	1.27	1.06	1.38
	DSA-positive status	0.32	0.42	<i>0.27</i>	0.47	0.78	0.53	0.70
All rejection	GRIT1	<i>0.79</i>	1.09	2.24	1.80	2.03	1.53	1.63
	RAT	<i>0.76</i>	1.09	2.68	2.06	2.44	1.67	1.82
	Rej-RAT	<i>0.76</i>	1.26	3.10	2.36	2.89	2.06	2.28
TCMR-related	QCAT	<i>0.75</i>	1.06	2.91	2.21	2.57	1.77	1.78
	TCB	<i>0.83</i>	1.25	3.63	3.01	3.10	2.08	1.95
	TCMR-RAT	<i>0.74</i>	0.98	2.96	2.25	2.45	1.55	1.52
Function	Mean LVEF	61	63	54	<i>45</i>	56	61	61
	Low LVEF≤55 fraction	0.19	<i>0.16</i>	0.44	0.82	0.41	0.26	0.20
	Classifier IoLVEF _{Prob}	0.17	<i>0.16</i>	0.45	0.48	0.41	0.23	0.21
Outcomes	Classifier Survival _{Prob}	0.81	0.84	0.68	<i>0.60</i>	0.72	0.82	0.88
	Event (any)	0.07	0.10	0.33	0.24	0.17	0.11	<i>0.02</i>
	Event (within 3 years post-biopsy)	0.06	0.10	0.21	0.15	0.10	0.10	<i>0.01</i>
	Number of failures (total = 117)	47	30	14	6	8	9	<i>3</i>
Kidney classifiers	ABMR _{Prob}	<i>0.10</i>	0.22	0.33	0.20	0.67	0.30	0.74
	g>0 _{Prob}	<i>0.26</i>	0.55	0.59	0.41	0.81	0.70	0.87
	ptc>0 _{Prob}	<i>0.10</i>	0.22	0.59	0.35	0.74	0.60	0.72
	TCMR _{Prob}	<i>0.03</i>	0.04	0.61	0.20	0.25	0.07	0.05
	i>1 _{Prob}	<i>0.06</i>	0.09	0.81	0.66	0.69	0.20	0.14
t>1 _{Prob}	<i>0.07</i>	0.09	0.79	0.67	0.69	0.16	0.13	

Bolding indicates the highest per row. Underline/italics is the lowest per row.

Table S7. Complete list of the molecular features of the 5 injury archetype groups in the N=3230 population

	Features	Normal	Mild-recent	Moderate-recent	Severe-recent	Late atrophy-fibrosis
Biopsy groups	N	1141 (35.3%)	794 (24.6%)	525 (16.3%)	149 (4.6%)	621 (19%)
	Days posttransplant (median)	454	143	119	65	1523
	Days posttransplant (mean)	1359	579	806	533	2083
Macrophages	AMAT1	<u>0.71</u>	0.96	1.20	2.25	1.54
	QCMAT	<u>0.68</u>	0.90	1.02	2.06	1.29
Atrophy-fibrosis	BAT	<u>0.80</u>	0.81	0.81	0.90	1.00
	IGT	0.81	0.77	<u>0.74</u>	1.36	2.50
Recent injury	cIRIT	<u>0.78</u>	0.84	0.98	1.31	0.98
	DAMP	<u>0.65</u>	1.00	0.76	1.25	0.78
	IRITD3	<u>0.77</u>	0.83	0.95	1.13	0.90
	IRITD5	<u>0.76</u>	0.87	1.11	1.29	0.95
	IRRAT	<u>0.67</u>	0.95	1.19	1.85	1.07
De-differentiation	HT1	0.86	0.85	0.73	<u>0.33</u>	0.69
	HT2	0.91	0.89	0.71	<u>0.05</u>	0.65
ABMR-related	ABMR-RAT	<u>0.87</u>	0.99	1.33	2.03	1.82
	NKB	1.04	<u>1.03</u>	1.25	1.33	1.46
	DSAST	<u>0.86</u>	0.88	1.03	0.93	1.12
	ABMR-RAT	<u>0.87</u>	0.99	1.33	2.03	1.82
	DSA positive status	0.37	<u>0.32</u>	0.45	0.55	0.58
All-rejection-related	GRIT1	<u>0.81</u>	0.95	1.21	1.90	1.63
	RAT	<u>0.80</u>	0.95	1.23	2.20	1.83
	Rej-RAT	<u>0.85</u>	1.05	1.44	2.58	2.18
	QCAT	<u>0.79</u>	0.92	1.22	2.19	1.88
	TCB	<u>0.86</u>	1.05	1.31	2.41	2.37
	TCMR-RAT	<u>0.73</u>	0.87	1.09	2.25	1.77
Function-related	LVEF	61	63	63	56	<u>55</u>
	Low LVEF≤55 fraction	0.20	<u>0.12</u>	0.16	0.35	0.39
	Classifier IoLVEF _{Prob}	0.18	<u>0.13</u>	0.15	0.35	0.32
Outcomes	Classifier Survival _{Prob}	0.83	0.83	0.86	<u>0.71</u>	0.75
	Event (any)	0.07	0.06	<u>0.04</u>	0.18	0.18
	Event (within 3 years post-biopsy)	0.07	0.06	<u>0.02</u>	0.14	0.15
	Number of failures (total = 117)	31	31	<u>7</u>	18	30
Kidney classifiers	ABMR _{Prob}	<u>0.19</u>	0.17	0.33	0.36	0.44
	g>0 _{Prob}	<u>0.38</u>	0.41	0.52	0.55	0.64
	ptc>0 _{Prob}	<u>0.18</u>	0.19	0.33	0.49	0.51
	TCMR _{Prob}	<u>0.03</u>	0.04	0.04	0.24	0.13
	i>1 _{Prob}	<u>0.06</u>	0.07	0.09	0.43	0.33
	t>1 _{Prob}	<u>0.07</u>	<u>0.07</u>	0.08	0.37	0.32

Bolding indicates the highest per row. Underline/italics is the lowest per row.

Table S8. Complete list of the molecular features of the 5 injury archetypes in 1564 biopsies classified as 'No rejection' by rejection archetypal analysis						
Biopsy groups	Features	Normal	Mild-recent	Moderate-recent	Severe-recent	Late atrophy-fibrosis
	N	723 (46%)	456 (29%)	231 (14.7%)	45 (2.8%)	109 (6.9%)
	Time posttransplant (median)	365	<u>11</u>	46	28.5	1674
	Time posttransplant (mean)	1212	567	338	<u>234</u>	2058
Macrophages	AMAT1	<u>0.62</u>	0.85	1.06	2.21	1.22
	QCMAT	<u>0.60</u>	0.82	0.91	2.08	1.01
Atrophy-fibrosis	BAT	0.78	0.79	<u>0.77</u>	0.78	0.93
	IGT	0.76	0.68	<u>0.57</u>	0.79	2.43
Recent injury	cIRIT	<u>0.76</u>	0.82	0.97	1.42	0.90
	DAMP	<u>0.64</u>	1.00	0.77	1.36	0.74
	IRITD3	<u>0.77</u>	0.81	0.96	1.23	0.86
	IRITD5	<u>0.74</u>	0.84	1.12	1.46	0.89
	IRRAT	<u>0.62</u>	0.89	1.20	2.16	0.96
De-differentiation	HT1	0.88	0.87	0.73	<u>0.19</u>	0.76
	HT2	0.93	0.91	0.69	<u>-0.17</u>	0.75
ABMR-related	ABMR-RAT	<u>0.64</u>	0.75	0.85	1.32	1.26
	NKB	0.89	<u>0.88</u>	<u>0.88</u>	<u>0.88</u>	0.99
	DSAST	<u>0.77</u>	0.79	0.81	0.62	0.86
	DSA-positive status	0.30	<u>0.28</u>	0.31	0.50	0.52
All-rejection-related	GRIT1	<u>0.66</u>	0.78	0.90	1.35	1.27
	RAT	<u>0.61</u>	0.74	0.85	1.54	1.30
	Rej-RAT	<u>0.56</u>	0.75	0.87	1.69	1.49
TCMR-related	QCAT	<u>0.60</u>	0.71	0.87	1.44	1.32
	TCB	<u>0.64</u>	0.81	0.90	1.44	1.79
	TCMR-RAT	<u>0.59</u>	0.72	0.81	1.61	1.29
Function-related	LVEF	60.61	61.43	62.78	<u>56.00</u>	<u>56.12</u>
	Low LVEF≤55 fraction	0.21	0.16	<u>0.12</u>	0.27	0.30
	Classifier score IoLVEF_{Prob}	0.17	<u>0.13</u>	0.17	0.27	0.32
Outcomes	Classifier Survival_{Prob}	0.81	0.82	0.83	0.71	<u>0.68</u>
	Event (any)	0.06	0.05	<u>0.04</u>	0.23	0.17
	Event (within 3 years post-biopsy)	0.07	0.04	<u>0.02</u>	0.21	0.19
	Number of failures (total = 117)	18	14	4	6	5
Kidney rejection classifiers	ABMR_{Prob}	<u>0.09</u>	<u>0.09</u>	0.10	0.13	0.15
	g>0_{Prob}	0.25	0.26	0.25	<u>0.23</u>	0.33
	ptc>0_{Prob}	<u>0.09</u>	0.10	0.10	0.15	0.20
	TCMR_{Prob}	<u>0.03</u>	<u>0.03</u>	<u>0.03</u>	0.06	0.07
	i>1_{Prob}	<u>0.04</u>	0.05	0.05	0.19	0.16
	t>1_{Prob}	<u>0.05</u>	0.06	0.06	0.11	0.16

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