

Figure S1. Receiver operating characteristic (ROC) Classification of NeoVanc samples using the Sep3 gene signature with time from treatment initiation on X-axis and classifier output scores on Y-axis. Sample points colored according to the assigned class. Black loess curve indicates the overall trend. Light gray lines indicate actual score trajectory for patients with at least 4 samples. Black asterisks mark the time of initiation of any pre-study vancomycin next to the corresponding patient. Patients misclassified at T_R identified. The red dashed line represents class boundary derived from Sep3 discovery cohort. $n = 113$.

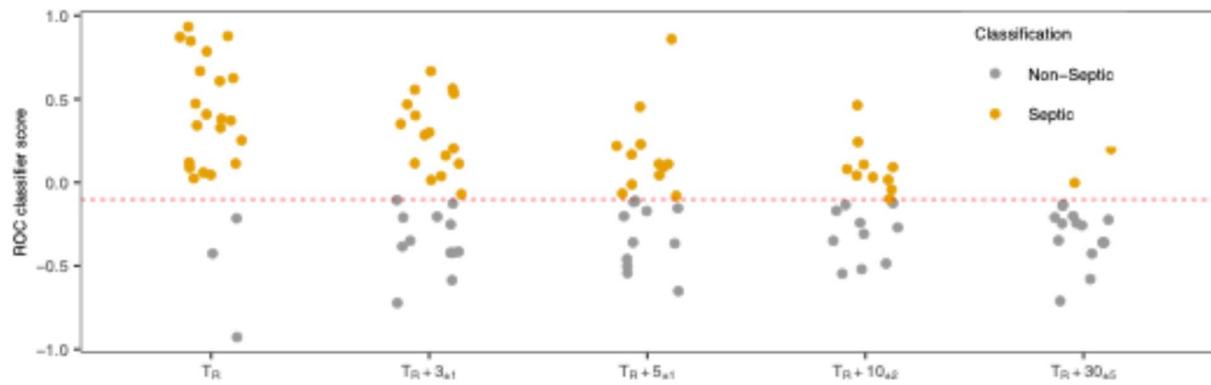


Figure S2. ROC classification of NeoVanc samples using the Sepsis Meta Score (SMS) gene signature. Sample collection time points are shown on the X-axis with the classifier output scores on the Y-axis. Sample points are colored according to the assigned class at each time point (T_R : $n = 24$; $T_R + 3$ days: $n = 28$; $T_R + 5$ days: $n = 23$; $T_R + 10$ days: $n = 20$; $T_R + 30$ days: $n = 18$). The red dashed line represents class boundary derived from Sep3 discovery cohort.

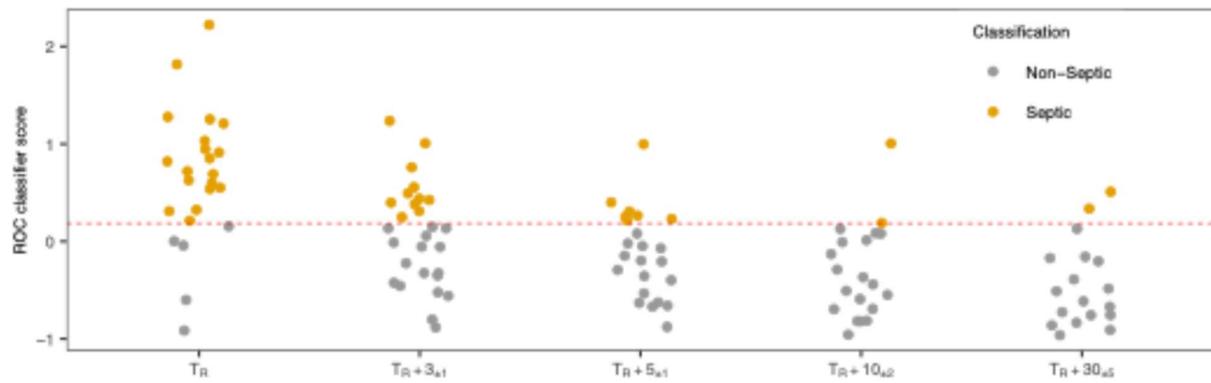


Figure S3. ROC classification of NeoVanc samples using the Yan *et al.* gene signature. Sample collection time points are shown on the X-axis with the classifier output scores on the Y-axis. Sample points are colored according to the assigned class at each time point (T_R : $n = 24$; $T_R + 3$ days: $n = 28$; $T_R + 5$ days: $n = 23$; $T_R + 10$ days: $n = 20$; $T_R + 30$ days: $n = 18$). The red dashed line represents class boundary derived from Sep3 discovery cohort.

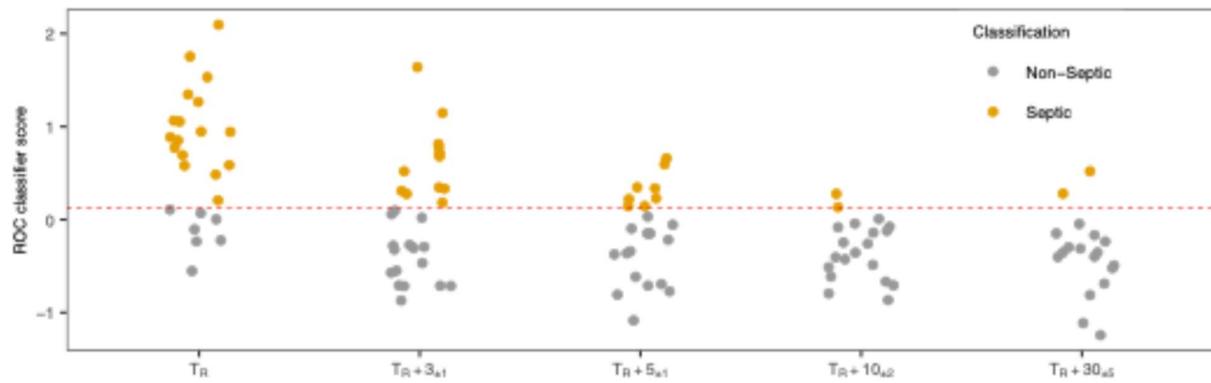


Figure S4. ROC classification of NeoVanc samples using the Bai *et al.* gene signature. Sample collection time points are shown on the X-axis with the classifier output scores on the Y-axis. Sample points are colored according to the assigned class at each time point (T_R : $n = 24$; $T_R + 3$ days: $n = 28$; $T_R + 5$ days: $n = 23$; $T_R + 10$ days: $n = 20$; $T_R + 30$ days: $n = 18$). The red dashed line represents class boundary derived from Sep3 discovery cohort.

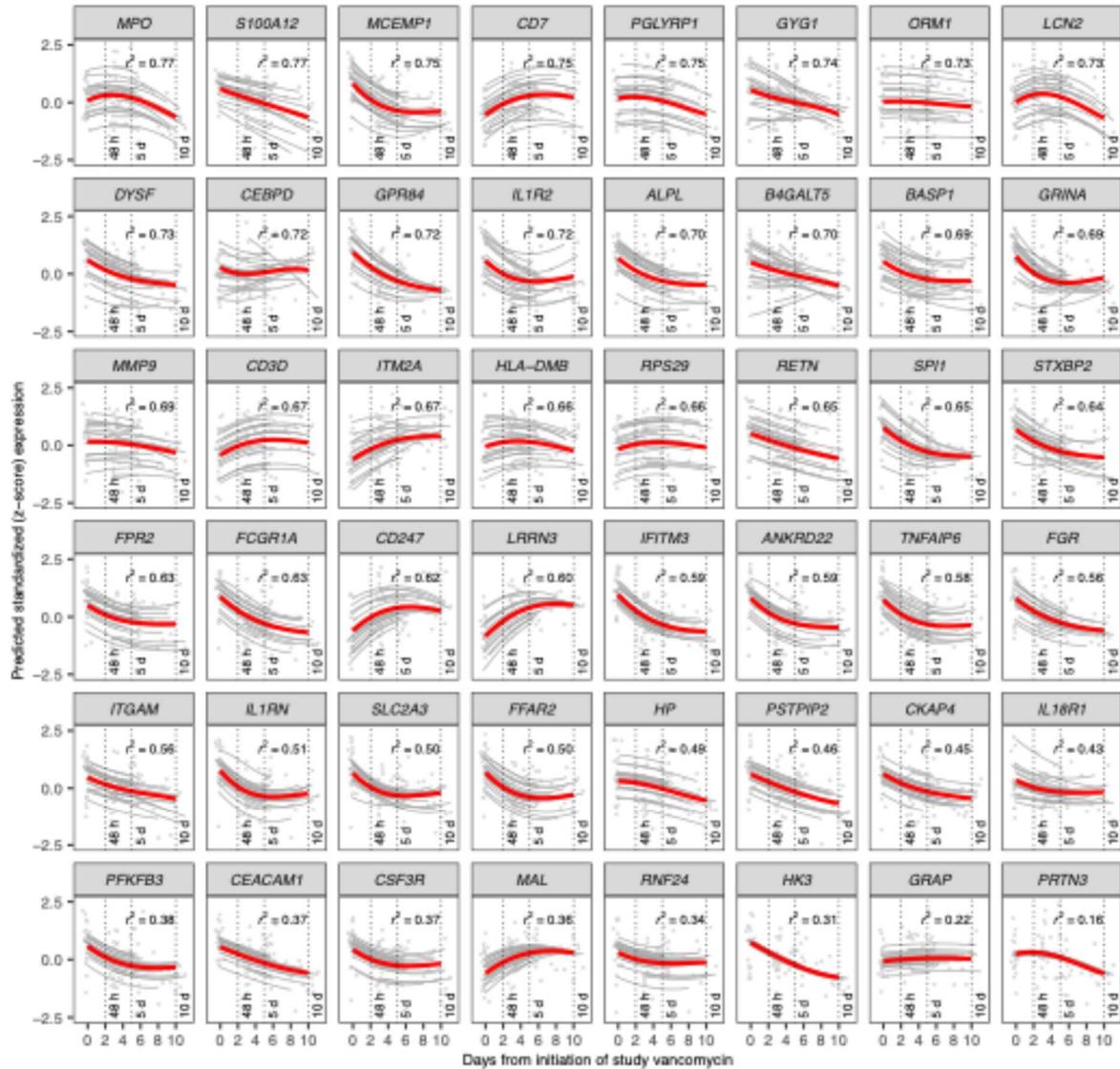


Figure S5. Gene expression trajectories for Sep3 genes in the 10 days following vancomycin treatment. X-axis shows time in hours. Y-axis shows scaled expression (z-scored). Red line represents the mean (fixed effects) model. Light gray lines represent the modelled expression for individual patients (fixed plus random effects). Light gray crosses indicate observed data points (z-scored) for each patient. Conditional r^2 shown for each gene. $n = 89$.

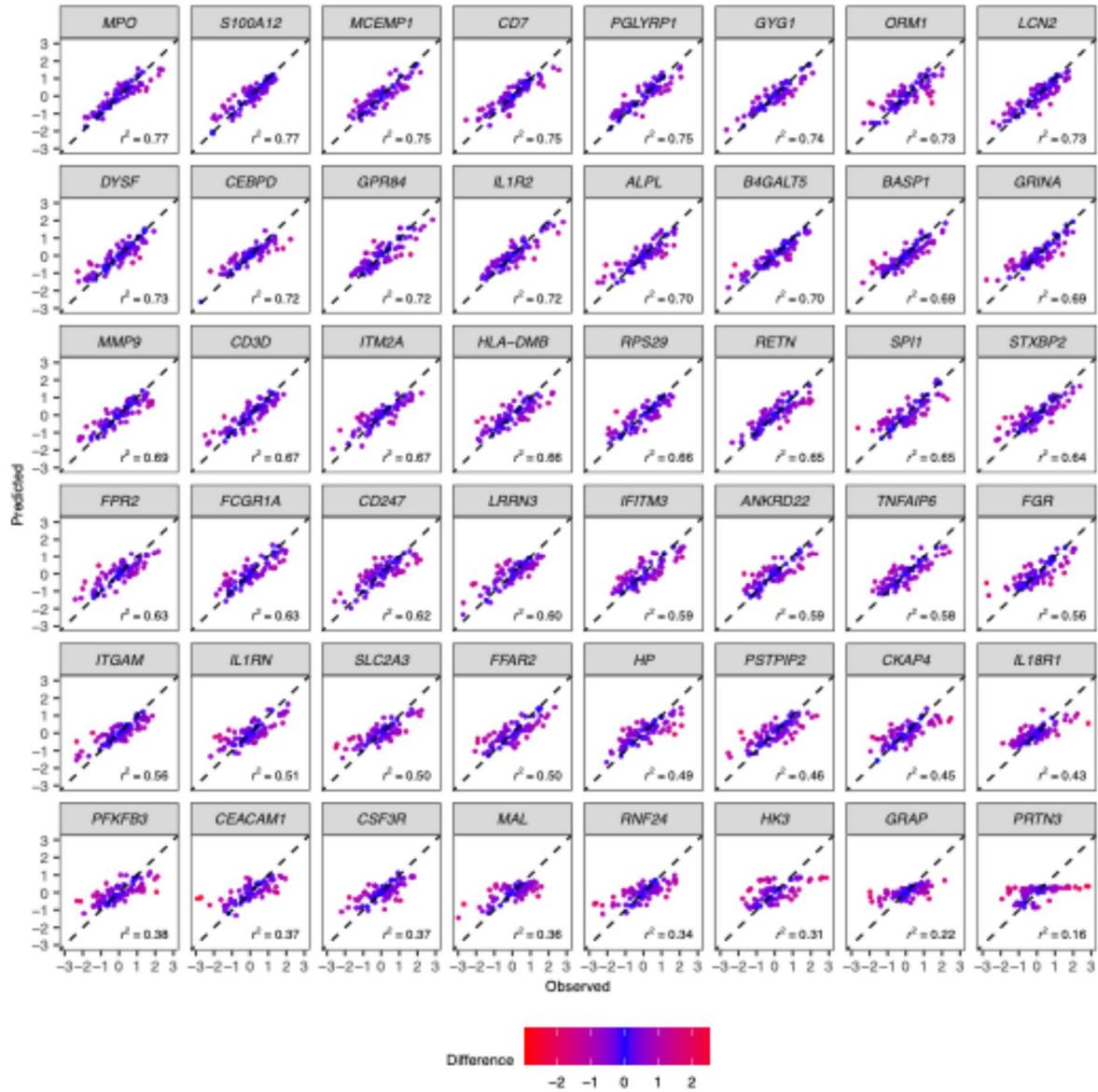


Figure S6. Gene-wise calibration plots of observed data on X-axis compared with LMRM model predicted points on Y-axis for Sep3 genes. Data is on a z-scored scale. Conditional r^2 shown for each gene. Color coding represents the difference, in units of standard deviation, between the observed and predicted values. $n = 89$.

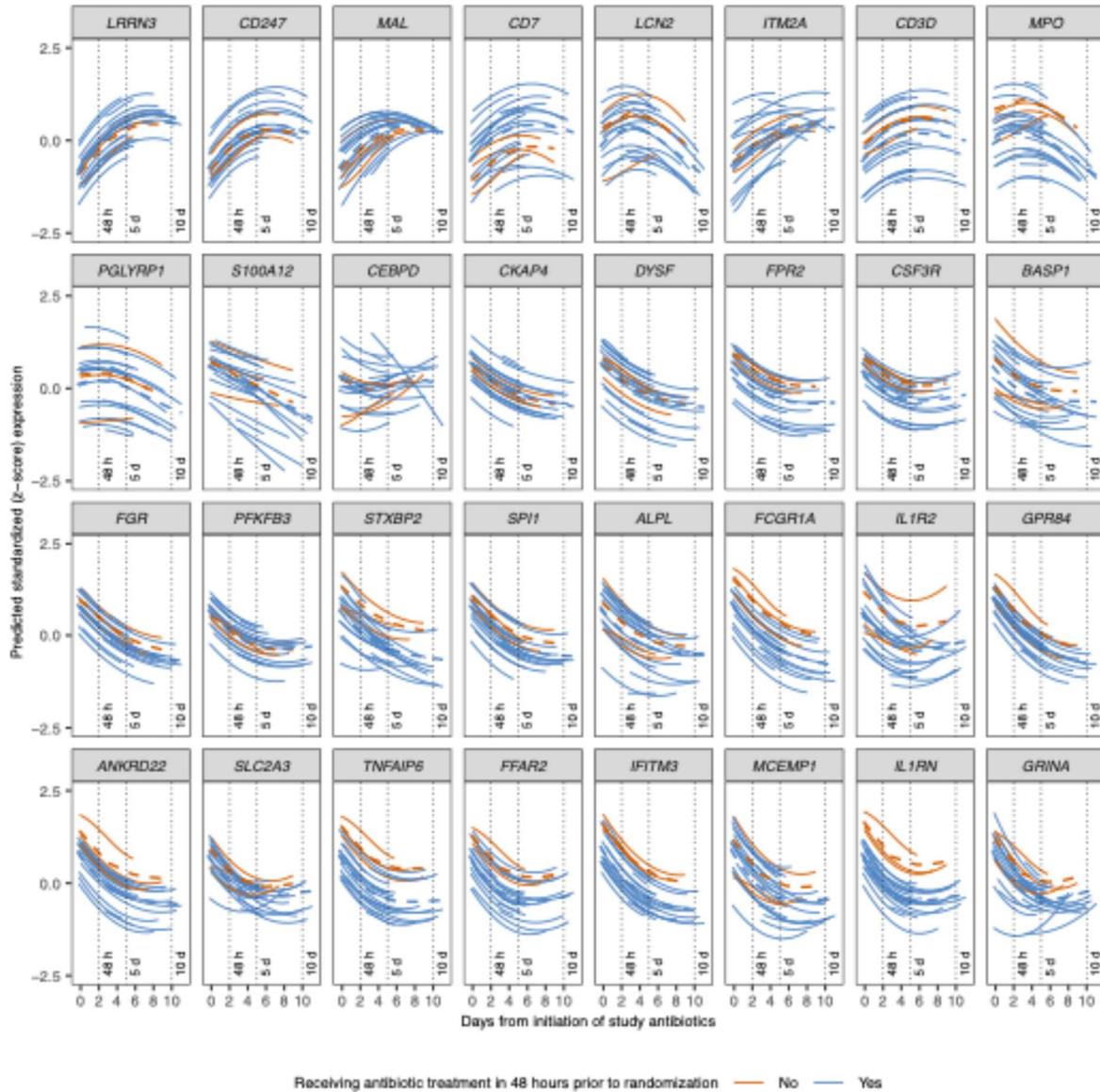


Figure S7. Impact of antibiotics administered prior to randomization on gene-wise expression trajectories for Sep3 genes with significant coefficients for time in the 10 days following vancomycin treatment. X-axis shows time in hours. Y-axis shows scaled expression (z-scored). Lines representing the modeled expression for individual patients (fixed plus random effects). Blue lines indicate patients who received antibiotics (which in all cases included one of the anti-staphylococcal antibiotics vancomycin or teicoplanin) during the 48 hours prior to randomization to the trial. Red lines represent patients that did not receive pre-study antibiotics. $n = 89$.

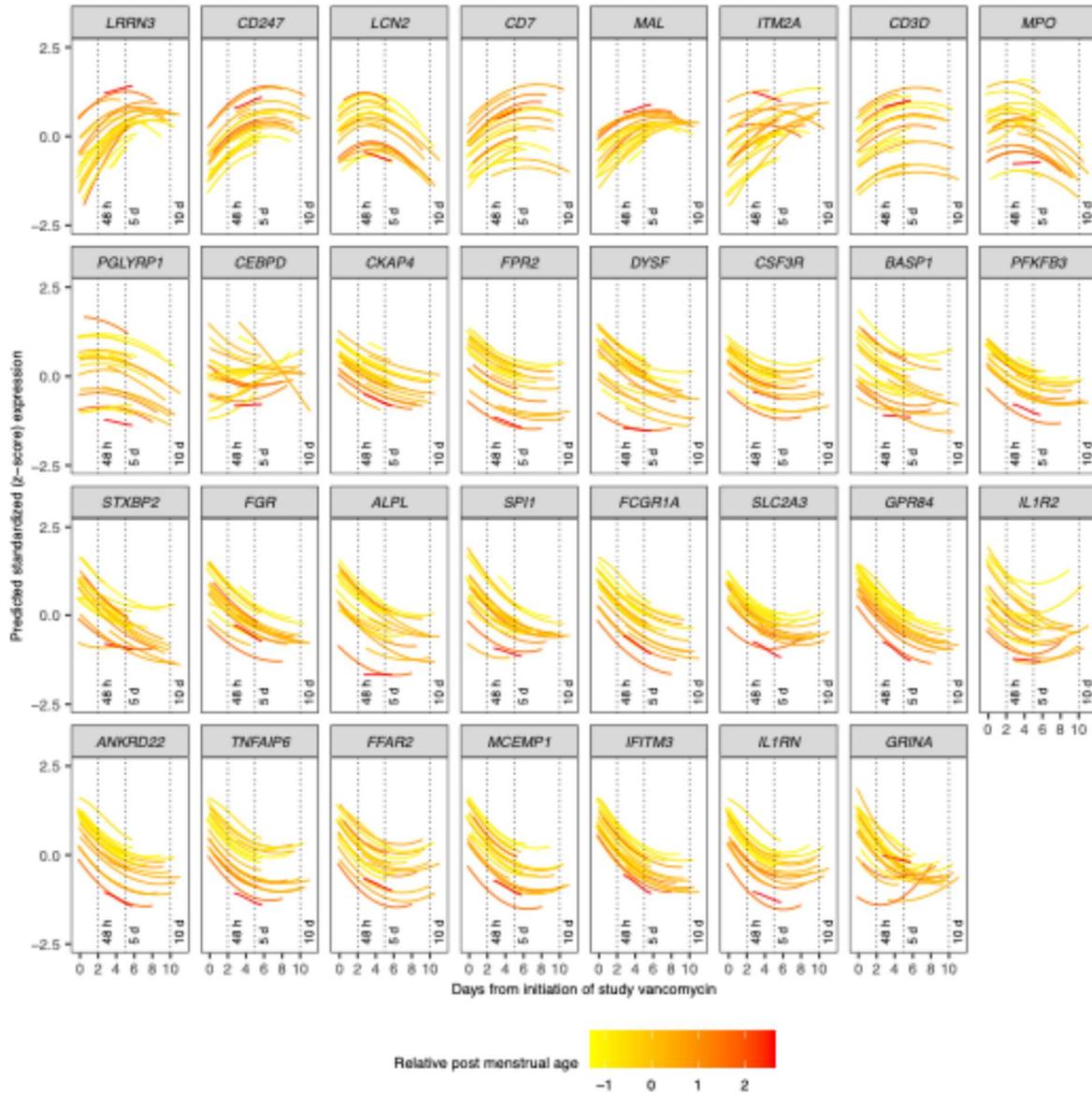


Figure S8. Impact of post menstrual age on gene-wise expression trajectories for Sep3 genes with significant coefficients for time in the 10 days following vancomycin treatment. X-axis shows time in hours. Y-axis shows scaled expression (z-score scale). Lines representing the modelled expression for individual patients (fixed plus random effects) are color coded based on relative post menstrual age. $n = 89$.

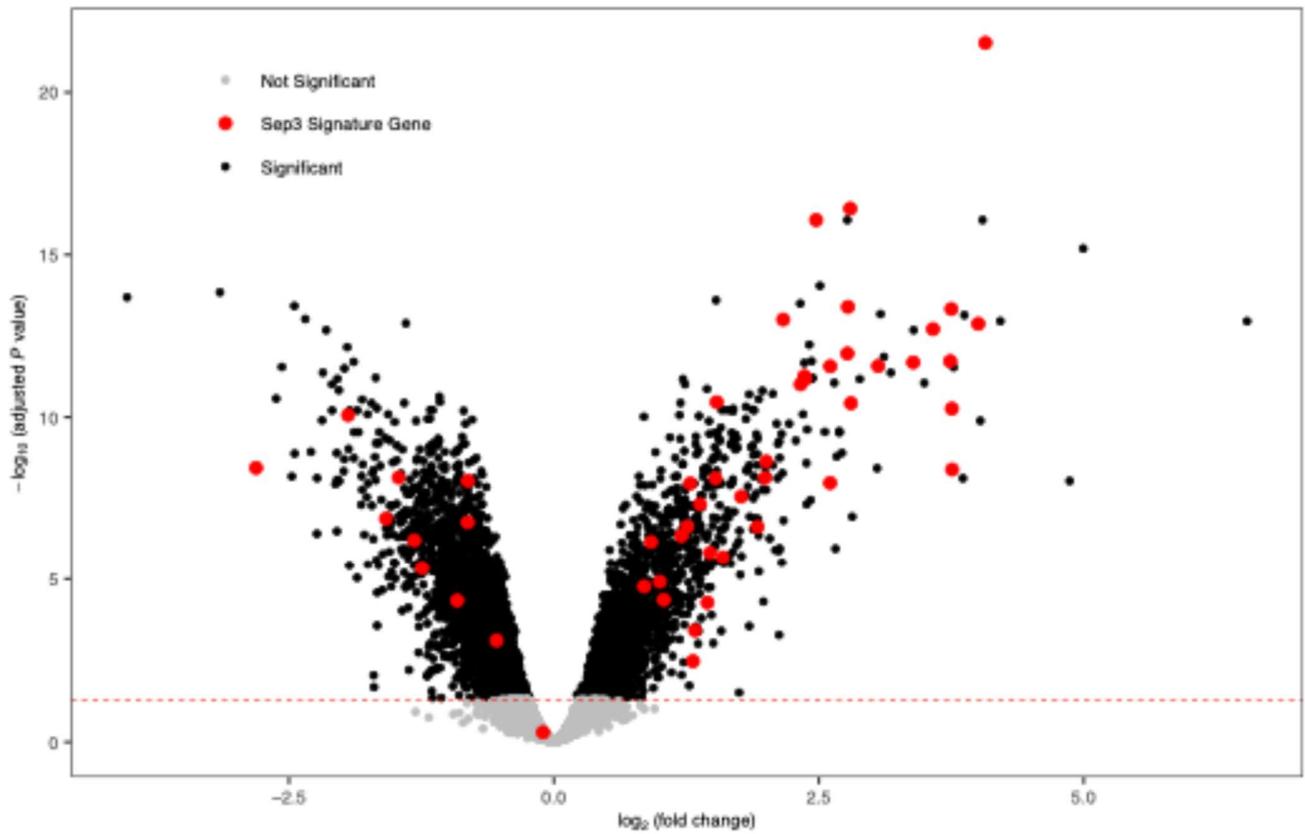


Figure S9. Volcano plot showing differentially expressed genes from the pediatric validation cohort day 1 sepsis ($n = 43$) compared with controls ($n = 18$). $\log_2(\text{fold change})$ in expression is given on the X-axis and $-\log_{10}(P \text{ value})$ is given on the Y-axis. Points representing genes with significant first-order coefficients at $\alpha = 0.05$ are colored black, with the Sep3 signature genes highlighted in red. The red dashed line indicates the significance threshold of $\alpha = 0.05$.

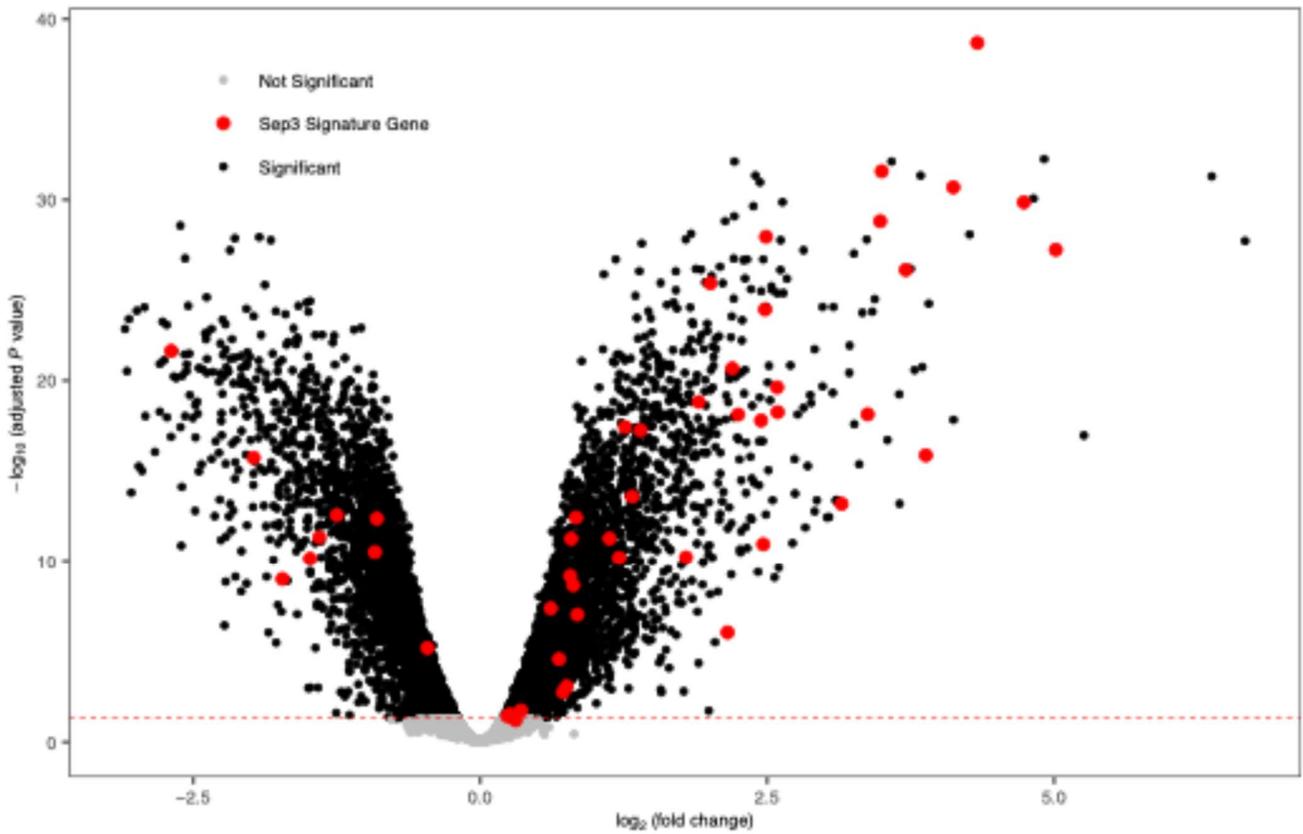


Figure S10. Volcano plot showing differentially expressed genes from the adult validation cohort onset of septic shock ($n = 50$) compared with controls ($n = 22$). $\log_2(\text{fold change})$ in expression is given on the X-axis and $-\log_{10}(P \text{ value})$ is given on the Y-axis. Points representing genes with significant first-order coefficients at 0.05 are colored black, with the Sep3 signature genes highlighted in red. The red dashed line indicates the significance threshold of $\alpha = 0.05$.

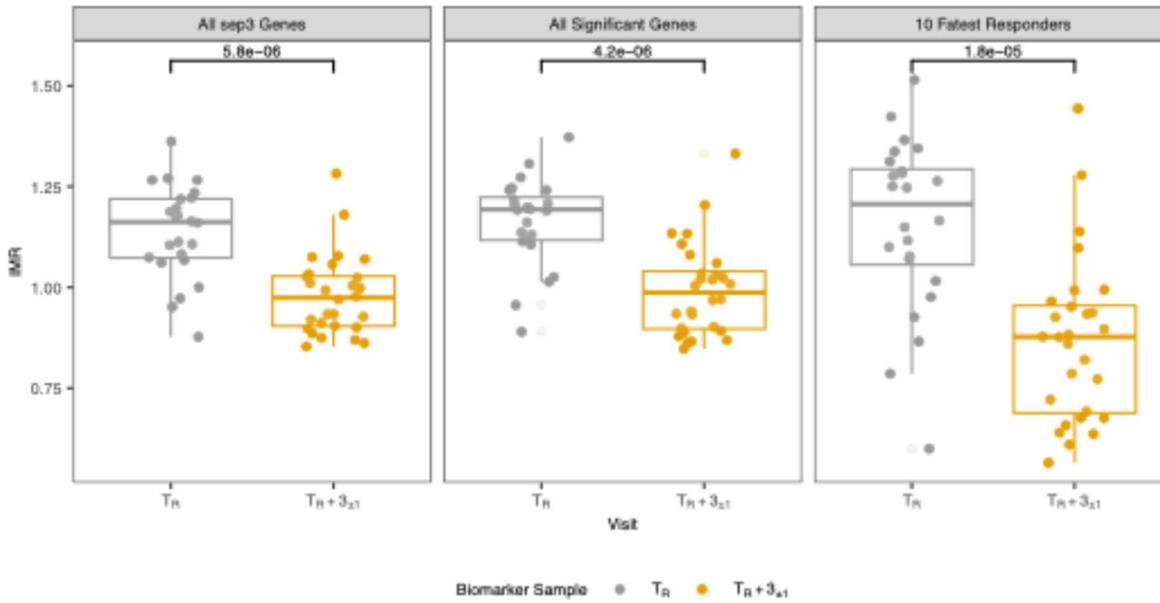


Figure S11. Comparison of the change in mean Immune Module Ratio (IMR) between T_R and $T_R + 3$ days for the NeoVanc cohort using three alternative gene signatures in the calculation: (1) All 48 Sep3 genes present in the NeoVanc data; (2) all genes with a significant regression coefficient in the LMRM analysis; (3) an optimized set of the five most strongly up-regulated and five most strongly down-regulated genes from the Sep3 signature. *P* values shown for the Wilcoxon rank sum test. $n = 113$.

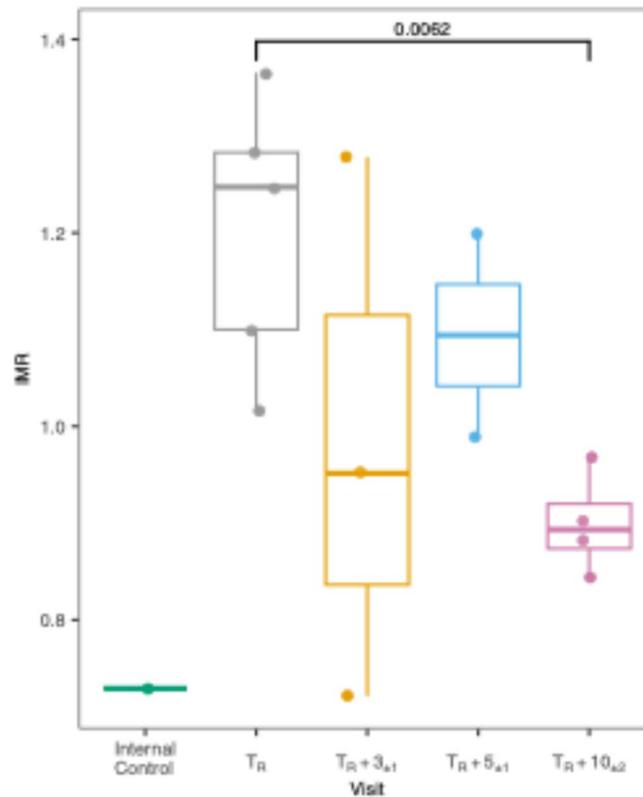


Figure S12. Distribution of IMR calculated with five most strongly up-regulated and five most strongly down-regulated Sep3 genes for the five NeoVanc patients that did not receive antibiotics in the 48 hours prior to randomization into the trial. t test for difference in mean expression between T_R and $T_R + 10$ days ($t = 4.4$, $P = 0.00062$). $T_R + 30$ days shown as an internal control, representing the assumed range of the IMR prior to onset of symptoms. Not all time points available for each of the five patients. $n = 15$.

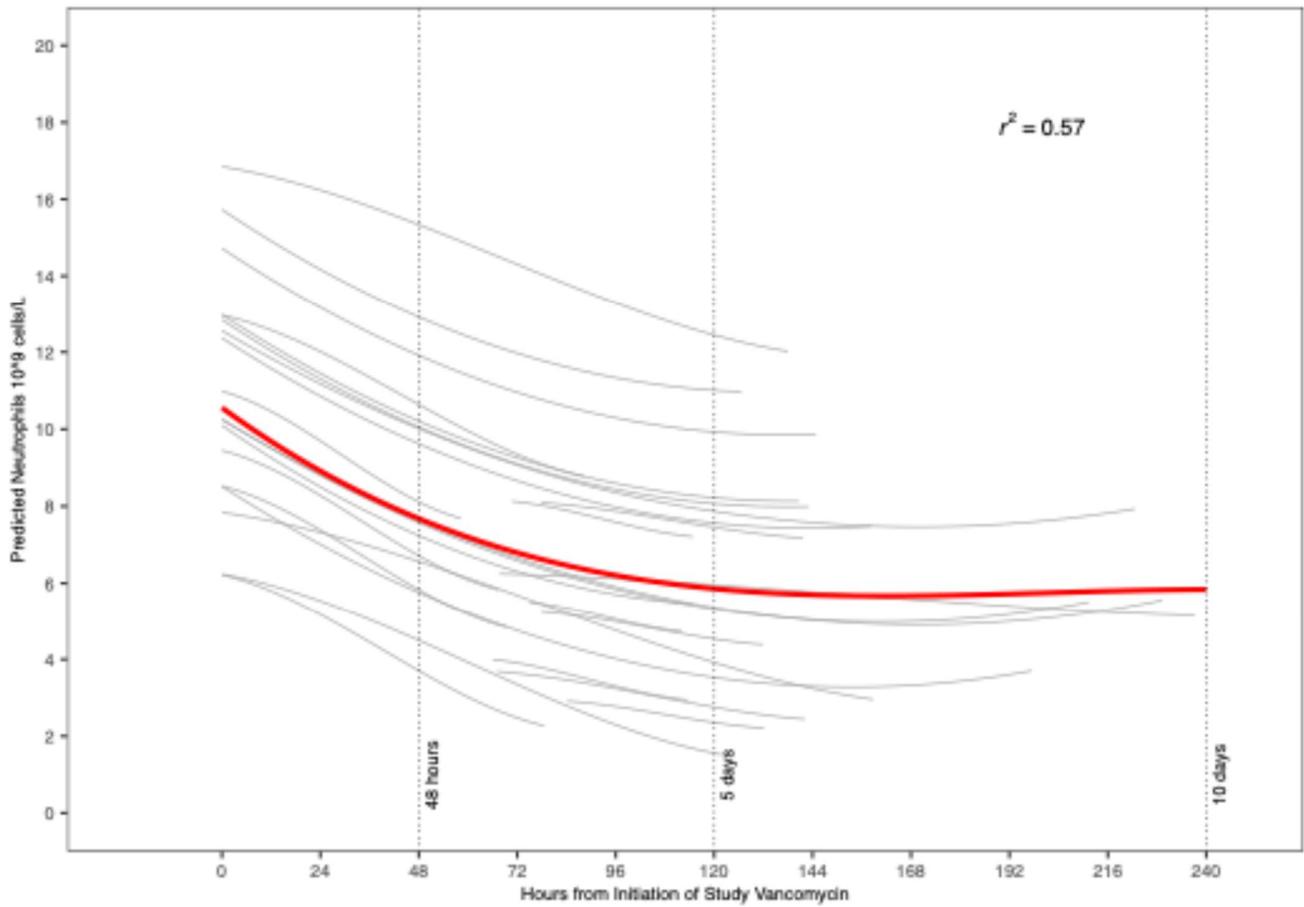


Figure S13. LMRM modelled neutrophil counts. X-axis shows time from treatment initiation in hours. Y-axis shows predicted neutrophil counts in 10⁹ cells/L. Red line represents the mean (fixed effects) model. Light gray lines represent the modelled expression for individual patients (fixed plus random effects). Conditional r^2 shown. $n = 113$.

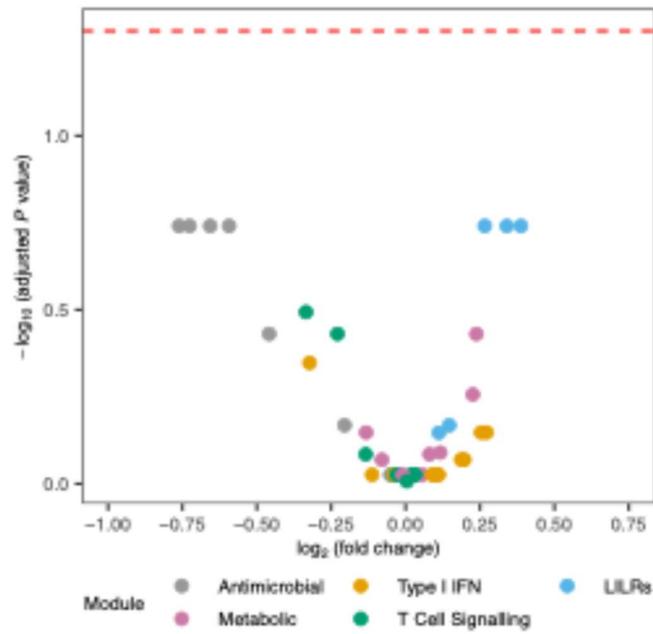


Figure S14. Differential expression of 47 representative genes across the five gene modules between day 3 and day 1 sepsis non-survivors in the adult validation cohort. Points colored by gene module. The red dashed line indicates the significance threshold of $\alpha = 0.05$. $n = 17$.

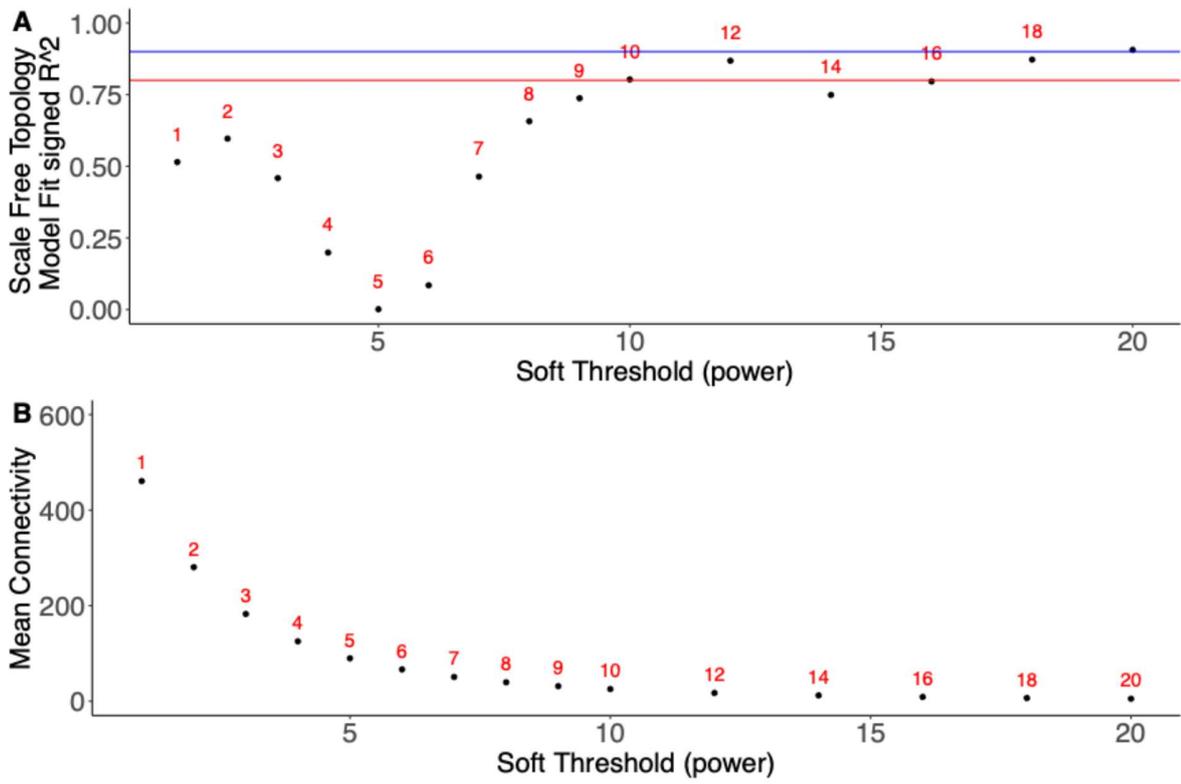


Figure S15. (A) Power value on the X-axis with r^2 value of the scale-free topology model fit on the Y-axis; red and blue lines represent r^2 values of 0.8 and 0.9, respectively. **(B)** Power value on the X-axis with mean connectivity of the genes on the Y-axis. $n = 113$.

Table S1. Published sepsis gene signatures used in classifiers and diagnostic scores to differentiate healthy from septic neonatal infants.

	Signature Genes	Discovery Cohort	Validation Cohort	Reference
Sep3	<i>ALPL, ANKRD22, B4GALT5, BASP1, CD247, CD3D, CD7, CEACAM1, CEBPD, CKAP4, CSF3R, DYSF, FCGR1A, FFAR2, FGR, FPR2, GPR84, GRAP, GRINA, GYG1, HK3, HLA-DMB, HP, IFITM3, IL18R1, IL1R2, IL1RN, ITGAM, ITM2A, LCN2, LIME1, LRRN3, MAL, MCEMP1, MMP9, MPO, ORM1, PFKFB3, PGLYRP1, PRTN3, PSTPIP2, RETN, RNF24, RPS29, S100A12, SLC2A3, SPI1, SRCAP, STXBP2, TNFAIP6, TRAJ17, TRBV28</i>	Neonates (GSE25504)	Neonates (GSE25504V)	(13)
Sepsis Meta Score	<i>BATF, C3AR1, CEACAM1, FAM214A, GNA15, HLA-DPB1, MTCH1, NMRK1, RPGRIP1, TGFBI, ZDHHC19</i>	Adult (GSE28750, GSE32707, GSE40012, Glue Grant-Trauma), Pediatric (GSE66099)	Neonates (EMTAB-4785, GSE25504, GSE69686)	(10, 16)
Yan <i>et al.</i>	<i>CD3G, ID3, OSCAR, PSTPIP2, SLC2A3</i>	Neonates (GSE25504, GSE26440)	Neonates (GSE25504-V, GSE69686)	(18)
Bai <i>et al.</i>	<i>ANKRD22, CD247, CD3G, CD8B, CST7, GPR84, MAL, SIRPG</i>	Neonates (GSE25504)	Neonates (Unpublished)	(19)

Table S2. NeoVanc trial inclusion criteria.

Criteria

1. Postnatal age ≤ 90 days at randomization AND
2. Postnatal age ≥ 72 h at onset of sepsis AND
3. Clinical sepsis as defined by the presence of any three clinical or laboratory criteria (table S3), in the 24 h before randomization

OR

Confirmed, significant bacterial sepsis as defined by positive culture with a Gram-positive bacterium from a normally sterile site and at least one clinical or one laboratory criterion from the Table S3, in the 24 h before randomization.

Table S3. Adapted European Medicines Agency neonatal sepsis criteria.

Criteria Type	Criteria Thresholds
Clinical	<ol style="list-style-type: none">1. Hyperthermia or hypothermia2. Hypotension or impaired peripheral perfusion or mottled skin3. Apnea or increased oxygen requirement or increased requirement for ventilatory support4. Bradycardic episodes or tachycardia5. Worsening feeding intolerance or abdominal distension6. Lethargy or hypotonia or irritability
Laboratory	<ol style="list-style-type: none">1. White blood cell (WBC) count < 4 or $> 20 \times 10^9$ cells/L2. Immature to total neutrophil ratio (I/T) > 0.23. Platelet count $< 100 \times 10^9$ /L4. CRP > 10 mg/L5. Glucose intolerance as defined by a blood glucose value > 180 mg/dL (> 10 mmol/L) when receiving normal glucose amounts (8–15 g/kg/day)6. Metabolic acidosis as defined by a base excess (BE) < -10 mmol/L (< -10 mEq/L) or a blood lactate value > 2 mmol/L

Table S4. Schedule of biomarker sampling for NeoVanc clinical trial assessment visits.

Biomarker Sample	Visit Number	Visit Name	Sample Timing	Trial Arm
1	Visit 1a	Screening and randomization	Day 0	Std, Opt
2	Visit 3	Early on treatment	72 ± 8 h after initiation of study vancomycin	Std, Opt
3	Visit 4	End of allocated therapy (optimized arm)	5±1 days after initiation of study vancomycin	Std, Opt
4	Visit 5	End of allocated therapy (standard arm)	10±2 days after initiation of study vancomycin	Std only
5	Visit 7	Short-term follow-up visit	30±5 days after initiation of study vancomycin	Std, Opt
6	EVT	End of vancomycin therapy	End of primary course of vancomycin, only where treatment stopped earlier or later than outlined in the protocol	Std, Opt

Table S5. LMRM performance metrics for Sep3 genes. Genes categorized as significant if the *P* value for the first, second, or third order coefficient with time is less than 0.05. *n* = 89.

	Gene	<i>P</i> (t)	<i>P</i> (t²)	<i>P</i> (t³)	Marg. <i>r</i>²	Cond. <i>r</i>²	Sig at 0.05
1	<i>MCEMP1</i>	0.000002	0.000423	0.003859	0.241353	0.749159	TRUE
2	<i>IFITM3</i>	0.000010	0.009540	0.058420	0.394278	0.585928	TRUE
3	<i>IL1RN</i>	0.000012	0.000376	0.001282	0.254179	0.512246	TRUE
4	<i>GRINA</i>	0.000014	0.000518	0.005181	0.181214	0.689425	TRUE
5	<i>TNFAIP6</i>	0.000027	0.002247	0.009401	0.239585	0.580111	TRUE
6	<i>GPR84</i>	0.000039	0.033191	0.168445	0.335120	0.717890	TRUE
7	<i>ANKRD22</i>	0.000046	0.004848	0.013491	0.299482	0.585597	TRUE
8	<i>IL1R2</i>	0.000047	0.000967	0.006841	0.127699	0.715402	TRUE
9	<i>FCGR1A</i>	0.000070	0.036925	0.141446	0.354821	0.627849	TRUE
10	<i>FFAR2</i>	0.000072	0.003841	0.024492	0.192544	0.496530	TRUE
11	<i>CD247</i>	0.000184	0.008829	0.078543	0.140368	0.622268	TRUE
12	<i>LRRN3</i>	0.000311	0.032337	0.449829	0.274069	0.603828	TRUE
13	<i>ALPL</i>	0.000421	0.036388	0.154322	0.170274	0.702827	TRUE
14	<i>SPI1</i>	0.000554	0.036016	0.129518	0.192738	0.645054	TRUE
15	<i>SLC2A3</i>	0.000569	0.007628	0.027299	0.171655	0.502769	TRUE
16	<i>CD7</i>	0.000823	0.041957	0.281306	0.094094	0.747645	TRUE
17	<i>LCN2</i>	0.001903	0.000180	0.001427	0.165850	0.730910	TRUE
18	<i>CD3D</i>	0.001969	0.024248	0.095998	0.065939	0.672147	TRUE
19	<i>FGR</i>	0.002597	0.133302	0.317441	0.244616	0.561665	TRUE
20	<i>BASP1</i>	0.003225	0.043280	0.099366	0.117395	0.692063	TRUE
21	<i>DYSF</i>	0.003277	0.093701	0.185365	0.158129	0.729398	TRUE
22	<i>STXBP2</i>	0.003485	0.105612	0.250294	0.193471	0.635156	TRUE
23	<i>FPR2</i>	0.005715	0.071707	0.168683	0.099101	0.631427	TRUE
24	<i>PFKFB3</i>	0.007502	0.099857	0.255986	0.134177	0.375170	TRUE
25	<i>ITM2A</i>	0.009189	0.199992	0.562170	0.114831	0.670385	TRUE
26	<i>CSF3R</i>	0.015901	0.085207	0.193474	0.077637	0.365352	TRUE
27	<i>MAL</i>	0.016438	0.195810	0.583624	0.130486	0.355367	TRUE
28	<i>KAP4</i>	0.020417	0.204046	0.283166	0.188434	0.446608	TRUE
29	<i>MPO</i>	0.022988	0.004820	0.037730	0.180553	0.772439	TRUE
30	<i>CEBPD</i>	0.050487	0.008156	0.001107	0.244126	0.724891	TRUE
31	<i>S100A12</i>	0.057768	0.728615	0.673089	0.261176	0.771901	FALSE
32	<i>HK3</i>	0.058422	0.941566	0.516902	0.276224	0.305944	FALSE
33	<i>RPS29</i>	0.059204	0.080406	0.131491	0.018017	0.658999	FALSE
34	<i>ITGAM</i>	0.066396	0.312673	0.325324	0.176163	0.556616	FALSE
35	<i>IL18R1</i>	0.077717	0.200109	0.284399	0.054839	0.432043	FALSE
36	<i>GYG1</i>	0.080472	0.298418	0.137920	0.321132	0.742680	FALSE
37	<i>PSTPIP2</i>	0.084805	0.860274	0.797333	0.209012	0.457148	FALSE
38	<i>RETN</i>	0.090348	0.833291	0.930071	0.157173	0.652294	FALSE
39	<i>RNF24</i>	0.095318	0.199566	0.257208	0.043226	0.342238	FALSE
40	<i>B4GALT5</i>	0.107696	0.496619	0.424620	0.208931	0.697751	FALSE
41	<i>CEACAM1</i>	0.146120	0.880157	0.799625	0.157313	0.369060	FALSE
42	<i>HLA-DMB</i>	0.149200	0.132918	0.262849	0.033671	0.660758	FALSE
43	<i>PGLYRP1</i>	0.305531	0.047030	0.068333	0.084479	0.747378	TRUE
44	<i>PRTN3</i>	0.450134	0.113092	0.107145	0.134617	0.161644	FALSE
45	<i>GRAP</i>	0.715579	0.843963	0.956911	0.003963	0.217027	FALSE
46	<i>ORM1</i>	0.780814	0.507046	0.427147	0.004965	0.734597	FALSE
47	<i>MMP9</i>	0.892517	0.556366	0.724805	0.058257	0.686908	FALSE
48	<i>HP</i>	0.939175	0.301453	0.213513	0.097873	0.493888	FALSE

Table S6. Sep3 genes present in NeoVanc dataset. Functional class assignments in accordance with (13).

	Gene name	Functional Class
1	<i>CD247</i>	Adaptive
2	<i>CD3D</i>	Adaptive
3	<i>CD7</i>	Adaptive
4	<i>GRAP</i>	Adaptive
5	<i>HLA-DMB</i>	Adaptive
6	<i>ITM2A</i>	Adaptive
7	<i>LRRN3</i>	Adaptive
8	<i>MAL</i>	Adaptive
9	<i>ANKRD22</i>	Innate
10	<i>BASP1</i>	Innate
11	<i>CEACAM1</i>	Innate
12	<i>CEBPD</i>	Innate
13	<i>CKAP4</i>	Innate
14	<i>CSF3R</i>	Innate
15	<i>DYSF</i>	Innate
16	<i>FCGR1A</i>	Innate
17	<i>FGR</i>	Innate
18	<i>HP</i>	Innate
19	<i>IFITM3</i>	Innate
20	<i>IL18R1</i>	Innate
21	<i>IL1R2</i>	Innate
22	<i>IL1RN</i>	Innate
23	<i>ITGAM</i>	Innate
24	<i>LCN2</i>	Innate
25	<i>MCEMP1</i>	Innate
26	<i>MMP9</i>	Innate
27	<i>ORM1</i>	Innate
28	<i>PGLYRP1</i>	Innate
29	<i>PRTN3</i>	Innate
30	<i>PSTPIP2</i>	Innate
31	<i>RNF24</i>	Innate
32	<i>S100A12</i>	Innate
33	<i>SPI1</i>	Innate
34	<i>TNFAIP6</i>	Innate
35	<i>ALPL</i>	Metabolic
36	<i>B4GALT5</i>	Metabolic
37	<i>FFAR2</i>	Metabolic
38	<i>FPR2</i>	Metabolic
39	<i>GPR84</i>	Metabolic
40	<i>GRINA</i>	Metabolic
41	<i>GYG1</i>	Metabolic
42	<i>HK3</i>	Metabolic
43	<i>MPO</i>	Metabolic
44	<i>PFKFB3</i>	Metabolic
45	<i>RETN</i>	Metabolic
46	<i>RPS29</i>	Metabolic
47	<i>SLC2A3</i>	Metabolic
48	<i>STXBP2</i>	Metabolic

Table S7. Comparison of first order regression coefficients β and r^2 values for genes with a significant time coefficient, with and without the administration of pre-study antibiotics (PSA) included as a factor in the model. β_{psa} denotes the coefficient for PSA, P_{psa} is the P value for PSA in the model. β_{time} and $\beta_{timepsa}$ are the coefficients for time, with and without PSA in the model respectively. r^2 and r^2_{psa} are the marginal r^2 values with and without PSA in the model. $n = 89$. PSA is significant for two genes (*IL1RN* and *TNFAIP6*) at $\alpha < 0.05$ (highlighted in bold).

Gene	β_{psa}	P_{psa}	β_{time}	$\beta_{timepsa}$	r^2	r^2_{psa}
<i>GRINA</i>	-0.4658	0.2395	-0.0193	-0.0193	0.1812	0.2030
<i>IL1RN</i>	-0.9730	0.0157	-0.0191	-0.0189	0.2542	0.3350
<i>MCCEMP1</i>	-0.3698	0.4447	-0.0183	-0.0181	0.2414	0.2442
<i>IFITM3</i>	-0.7170	0.0947	-0.0172	-0.0170	0.3943	0.4001
<i>FFAR2</i>	-0.6571	0.1320	-0.0169	-0.0168	0.1925	0.2352
<i>SLC2A3</i>	-0.2691	0.4936	-0.0164	-0.0161	0.1717	0.1701
<i>TNFAIP6</i>	-0.8952	0.0360	-0.0164	-0.0164	0.2396	0.3131
<i>ANKRD22</i>	-0.6561	0.1166	-0.0160	-0.0160	0.2995	0.3287
<i>IL1R2</i>	-0.6613	0.1783	-0.0158	-0.0157	0.1277	0.1620
<i>GPR84</i>	-0.3705	0.2975	-0.0154	-0.0159	0.3351	0.4287
<i>FCGR1A</i>	-0.7116	0.0744	-0.0147	-0.0146	0.3548	0.3960
<i>SPI1</i>	-0.3287	0.4383	-0.0142	-0.0134	0.1927	0.2338
<i>ALPL</i>	-0.2024	0.6920	-0.0135	-0.0135	0.1703	0.1670
<i>FGR</i>	-0.2184	0.5878	-0.0127	-0.0118	0.2446	0.2564
<i>STXBP2</i>	-0.7160	0.1056	-0.0125	-0.0124	0.1935	0.2268
<i>PFKFB3</i>	0.0399	0.9274	-0.0121	-0.0121	0.1342	0.1311
<i>BASP1</i>	-0.2645	0.6230	-0.0117	-0.0116	0.1174	0.1160
<i>FPR2</i>	-0.4568	0.3256	-0.0109	-0.0106	0.0991	0.1349
<i>CSF3R</i>	-0.3985	0.3812	-0.0109	-0.0108	0.0776	0.0934
<i>DYSF</i>	-0.0394	0.9349	-0.0107	-0.0104	0.1581	0.1640
<i>CKAP4</i>	0.0426	0.9231	-0.0100	-0.0100	0.1884	0.1860
<i>CEBPD</i>	0.0372	0.9343	-0.0084	-0.0082	0.2441	0.2441
<i>PGLYRP1</i>	-0.2368	0.6780	0.0032	0.0033	0.0845	0.0847
<i>MPO</i>	-0.8967	0.0907	0.0076	0.0079	0.1806	0.2052
<i>CD3D</i>	-0.4162	0.4539	0.0105	0.0106	0.0659	0.0782
<i>ITM2A</i>	-0.0509	0.9114	0.0107	0.0107	0.1148	0.1123
<i>LCN2</i>	-0.4428	0.4097	0.0112	0.0114	0.1658	0.1672
<i>MAL</i>	0.0955	0.8081	0.0119	0.0129	0.1305	0.1292
<i>CD7</i>	0.5792	0.3302	0.0123	0.0121	0.0941	0.1320
<i>CD247</i>	0.1288	0.7745	0.0152	0.0159	0.1404	0.1682
<i>LRRN3</i>	0.0651	0.8800	0.0167	0.0160	0.2741	0.2412

Table S8. Comparison of first order regression coefficients β and r^2 values for genes with a significant time coefficient, with and without post menstrual age (PMA) included as a factor in the model. β_{pma} denotes the coefficient for PMA, P_{pma} is the P value for PMA in the model. β_{time} and $\beta_{timepma}$ are the coefficients for time, with and without PMA in the model respectively. r^2 and r^2_{pma} are the marginal r^2 values with and without PMA in the model. $n = 89$. PMA is significant for 13 of the genes (e.g. IL1RN, MCEMP1, SLC2A3, TNFAIP6) at $\alpha < 0.05$ (highlighted in bold).

Gene	β_{pma}	P_{pma}	β_{time}	$\beta_{timepma}$	r^2	r^2_{pma}
GRINA	-0.1144	0.3793	-0.0193	-0.0193	0.1812	0.2087
IL1RN	-0.3589	0.0060	-0.0191	-0.0186	0.2542	0.3682
MCEMP1	-0.3101	0.0225	-0.0183	-0.0168	0.2414	0.3520
IFITM3	-0.1905	0.1115	-0.0172	-0.0171	0.3943	0.4257
FFAR2	-0.1535	0.2949	-0.0169	-0.0168	0.1925	0.2141
SLC2A3	-0.2873	0.0183	-0.0164	-0.0153	0.1717	0.2458
TNFAIP6	-0.3562	0.0102	-0.0164	-0.0162	0.2396	0.3598
ANKRD22	-0.3831	0.0029	-0.0160	-0.0157	0.2995	0.4319
IL1R2	-0.3428	0.0318	-0.0158	-0.0157	0.1277	0.2298
GPR84	-0.3258	0.0022	-0.0154	-0.0156	0.3351	0.5179
FCGR1A	-0.3036	0.0184	-0.0147	-0.0145	0.3548	0.4372
SPI1	-0.2201	0.0775	-0.0142	-0.0144	0.1927	0.2658
ALPL	-0.3127	0.0503	-0.0135	-0.0136	0.1703	0.2638
FGR	-0.2300	0.0971	-0.0127	-0.0129	0.2446	0.2960
STXBP2	-0.2632	0.0640	-0.0125	-0.0125	0.1935	0.2490
PFKFB3	-0.2680	0.0529	-0.0121	-0.0119	0.1342	0.2047
BASP1	-0.2442	0.1528	-0.0117	-0.0116	0.1174	0.1688
FPR2	-0.4042	0.0201	-0.0109	-0.0101	0.0991	0.2414
CSF3R	-0.1805	0.2273	-0.0109	-0.0108	0.0776	0.1100
DYSF	-0.3420	0.0424	-0.0107	-0.0107	0.1581	0.2639
CKAP4	-0.2564	0.0671	-0.0100	-0.0096	0.1884	0.2433
CEBPD	-0.3189	0.0202	-0.0084	-0.0084	0.2441	0.2811
PGLYRP1	-0.3234	0.0794	0.0032	0.0033	0.0845	0.1707
MPO	-0.3219	0.0796	0.0076	0.0077	0.1806	0.2473
CD3D	0.1887	0.3048	0.0105	0.0105	0.0659	0.1014
ITM2A	0.1838	0.2262	0.0107	0.0109	0.1148	0.1446
LCN2	-0.2212	0.1485	0.0112	0.0126	0.1658	0.2234
MAL	0.1863	0.1177	0.0119	0.0116	0.1305	0.1605
CD7	0.2018	0.2275	0.0123	0.0120	0.0941	0.1464
CD247	0.3118	0.0271	0.0152	0.0156	0.1404	0.2700
LRRN3	0.3004	0.0042	0.0167	0.0178	0.2741	0.3404

Table S9. Spearman's Rank Correlation between IMR and laboratory measures commonly used to aid sepsis diagnosis in neonatal infants. $n = 113$.

Analyte	Spearman's σ	Confidence Interval	P value
Immune Module Ratio (IMR)	0.62	(0.47, 0.73)	< 0.001
C-Reactive Protein (CRP)	0.39	(0.20, 0.56)	< 0.001
Blood glucose	0.38	(0.19, 0.54)	< 0.001
Neutrophil count	0.34	(0.13, 0.51)	0.002

Table S10. Network nodes ranked by connectivity (degree) within the network at $T_R + 72$ hours. $n = 113$.

Innate-Metabolic		T Cell		Antimicrobial	
Gene	Degree	Gene	Degree	Gene	Degree
<i>FPR1</i>	47	<i>LEF1</i>	15	<i>CEACAM8</i>	10
<i>LILRB3</i>	45	<i>SLAMF6</i>	14	<i>LTF</i>	9
<i>ACSL1</i>	41	<i>CD28</i>	13	<i>BPI</i>	8
<i>AQP9</i>	38	<i>TCF7</i>	10	<i>CAMP</i>	5
<i>SOD2</i>	30	<i>FCMR</i>	7	<i>ERG</i>	5
<i>LIMK2</i>	30	<i>GNLY</i>	5	<i>CHI3L1</i>	4
<i>SIRPA</i>	27	<i>LRRN3</i>	5	<i>LCN2</i>	4
<i>PPP1R3B</i>	26	<i>EEIG1</i>	5	<i>OLR1</i>	4
<i>ADGRG3</i>	25	<i>S1PR1</i>	4	<i>OLFM4</i>	4
<i>IFI44</i>	24	<i>ICOS</i>	4	<i>MS4A3</i>	3
<i>TRIM25</i>	23	<i>CBLB</i>	4	<i>AFF2</i>	1
<i>TLR4</i>	21	<i>PRF1</i>	4	<i>TCN1</i>	1
<i>LILRB2</i>	21	<i>TESPA1</i>	4		
<i>APOL6</i>	21	<i>FCRL3</i>	3		
<i>MYD88</i>	19	<i>FGFBP2</i>	3		

Table S11. NeoVanc Trial Country Coordinators and Recruiting Site Principal Investigators and Co-Investigators.

NeoVanc Trial Country Coordinators	
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NeoVanc Independent Data Monitoring Committee	
	John van den Anker
	Corine Chazallon
	James Gray

Table S12. Simple Linear Regression r^2 and AIC values for Sep3 genes. $n = 89$.

Gene	r^2			AIC		
	linear	quadratic	cubic	linear	quadratic	cubic
<i>GPR84</i>	0.334	0.398	0.402	188.815	182.089	182.467
<i>IFITM3</i>	0.308	0.375	0.390	191.661	184.851	183.968
<i>FCGR1A</i>	0.261	0.333	0.332	196.661	189.893	190.958
<i>ANKRD22</i>	0.211	0.257	0.275	201.674	198.036	197.134
<i>HK3</i>	0.191	0.265	0.259	203.544	197.212	198.782
<i>MCEMP1</i>	0.154	0.241	0.256	206.902	199.634	199.138
<i>S100A12</i>	0.237	0.243	0.237	199.120	199.456	201.025
<i>LRRN3</i>	0.110	0.235	0.229	210.771	200.226	201.813
<i>TNFAIP6</i>	0.141	0.200	0.227	208.128	203.659	202.043
<i>FGR</i>	0.193	0.229	0.224	203.394	200.880	202.327
<i>IL1RN</i>	0.110	0.163	0.218	210.760	207.093	202.840
<i>GRINA</i>	0.069	0.162	0.207	214.201	207.164	203.978
<i>SPI1</i>	0.151	0.190	0.196	207.213	204.558	205.032
<i>STXBP2</i>	0.100	0.205	0.194	211.651	203.220	205.215
<i>RETN</i>	0.165	0.197	0.190	205.993	203.903	205.555
<i>PSTPIP2</i>	0.161	0.197	0.188	206.278	203.946	205.753
<i>ALPL</i>	0.118	0.191	0.186	210.078	204.477	205.912
<i>FFAR2</i>	0.061	0.151	0.172	214.874	208.220	207.212
<i>LCN2</i>	0.076	0.067	0.170	213.677	215.320	207.394
<i>CD247</i>	0.046	0.161	0.169	216.063	207.274	207.493
<i>DYSF</i>	0.137	0.171	0.164	208.442	206.400	207.974
<i>SLC2A3</i>	0.064	0.138	0.147	214.659	209.317	209.475
<i>IL1R2</i>	0.059	0.105	0.146	215.027	212.208	209.600
<i>CKAP4</i>	0.154	0.145	0.144	206.961	208.738	209.742
<i>CEACAM1</i>	0.122	0.154	0.144	209.743	207.881	209.749
<i>GYG1</i>	0.156	0.145	0.139	206.772	208.710	210.153
<i>MPO</i>	0.055	0.045	0.123	215.336	217.105	211.559
<i>FPR2</i>	0.073	0.121	0.117	213.883	210.810	212.132
<i>PFKFB3</i>	0.075	0.116	0.117	213.735	211.210	212.148
<i>ITM2A</i>	0.066	0.118	0.107	214.472	211.042	212.951
<i>ITGAM</i>	0.082	0.113	0.107	213.187	211.471	213.008
<i>B4GALT5</i>	0.118	0.113	0.104	210.126	211.488	213.226
<i>PRTN3</i>	0.091	0.078	0.098	212.420	214.418	213.722
<i>HP</i>	0.082	0.090	0.096	213.122	213.489	213.908
<i>BASP1</i>	0.068	0.101	0.096	214.262	212.527	213.927
<i>PGLYRP1</i>	0.089	0.077	0.085	212.566	214.562	214.810
<i>CD7</i>	0.011	0.085	0.073	218.837	213.839	215.787
<i>MAL</i>	0.020	0.079	0.069	218.117	214.349	216.108
<i>CSF3R</i>	0.023	0.061	0.067	217.900	215.821	216.265
<i>CEBPD</i>	0.010	0.050	0.063	218.909	216.719	216.614
<i>MMP9</i>	0.058	0.045	0.038	215.088	217.088	218.622
<i>RNF24</i>	0.025	0.022	0.019	217.755	218.937	220.088
<i>CD3D</i>	-0.006	0.016	0.018	220.129	219.407	220.177
<i>IL18R1</i>	0.014	0.019	0.009	218.573	219.155	220.887
<i>HLA-DMB</i>	0.004	-0.002	-0.009	219.335	220.759	222.223
<i>RPS29</i>	-0.011	-0.016	-0.018	220.463	221.812	222.942
<i>ORM1</i>	-0.004	-0.009	-0.018	219.957	221.330	222.961
<i>GRAP</i>	-0.014	-0.021	-0.035	220.672	222.169	224.162

Table S13. Intra-Class Correlation (ICC) for Sep3 genes. *n* = 89.

Gene	ICC
<i>RPS29</i>	0.647
<i>PGLYRP1</i>	0.587
<i>CD3D</i>	0.584
<i>MMP9</i>	0.555
<i>ORM1</i>	0.549
<i>RETN</i>	0.435
<i>HP</i>	0.416
<i>MPO</i>	0.414
<i>CD7</i>	0.411
<i>IL1R2</i>	0.411
<i>HLA-DMB</i>	0.397
<i>S100A12</i>	0.391
<i>DYSF</i>	0.386
<i>BASP1</i>	0.373
<i>FPR2</i>	0.371
<i>LCN2</i>	0.358
<i>ALPL</i>	0.328
<i>RNF24</i>	0.322
<i>CSF3R</i>	0.317
<i>IL18R1</i>	0.308
<i>TNFAIP6</i>	0.300
<i>CD247</i>	0.298
<i>MCEMP1</i>	0.289
<i>ITM2A</i>	0.265
<i>FFAR2</i>	0.259
<i>B4GALT5</i>	0.258
<i>PFKFB3</i>	0.232
<i>ITGAM</i>	0.229
<i>CEBPD</i>	0.217
<i>CEACAM1</i>	0.209
<i>PSTPIP2</i>	0.207
<i>LRRN3</i>	0.198
<i>GYG1</i>	0.191
<i>ANKRD22</i>	0.189
<i>GRAP</i>	0.183
<i>STXBP2</i>	0.181
<i>CKAP4</i>	0.173
<i>FCGR1A</i>	0.163
<i>SPI1</i>	0.155
<i>IL1RN</i>	0.141
<i>SLC2A3</i>	0.133
<i>IFITM3</i>	0.108
<i>GRINA</i>	0.082
<i>FGR</i>	0.078
<i>MAL</i>	0.043
<i>HK3</i>	0.011

Data file S1. Individual-level data