

Supplementary Table 1. Selected Human Molecular Signature Pathways Enriched in Genes Increased in Patients With and Without Linezolid-Associated Neuropathy

Gene Set Name	Pathway Database	Genes in Overlap / Genes in Gene Set	P-value	FDR q-value
Increased pathways in patients with linezolid-associated neuropathies				
Genes encoding cell cycle related targets of E2F transcription factors	Hallmark	23 / 200	1.72e ⁻¹⁶	4.68e ⁻¹³
Cell Cycle Mitotic	Reactome	30 / 560	4.09e ⁻¹²	4.04e ⁻⁰⁹
RNA Polymerase II Transcription	Reactome	49 / 1391	4.46e ⁻¹²	4.04e ⁻⁰⁹
Cell Cycle	Reactome	33 / 692	7.78e ⁻¹²	5.29e ⁻⁰⁹
Genes involved in the G2/M checkpoint, as in progression through the cell division cycle	Hallmark	17 / 200	1.96e ⁻¹⁰	1.07e ⁻⁰⁷
Cell Cycle Checkpoints	Reactome	18 / 291	9.40e ⁻⁰⁹	3.65e ⁻⁰⁶
Mitotic G1 Phase and G1/S Transition	Reactome	13 / 149	1.96e ⁻⁰⁸	6.68e ⁻⁰⁶
p53 Signaling Pathway	KEGG	9 / 63	8.35e ⁻⁰⁸	2.06e ⁻⁰⁵
Cell Cycle	KEGG	11 / 125	2.22e ⁻⁰⁷	4.65e ⁻⁰⁵
Transcriptional Regulation by TP53	Reactome	18 / 363	2.64e ⁻⁰⁷	5.13e ⁻⁰⁵
Mitotic Metaphase and Anaphase	Reactome	14 / 236	6.87e ⁻⁰⁷	9.87e ⁻⁰⁵
Mitotic Prometaphase	Reactome	13 / 203	7.26e ⁻⁰⁷	9.87e ⁻⁰⁵
Cell cycle	Wikipathways	10 / 120	1.31e ⁻⁰⁶	1.69e ⁻⁰⁴
Resolution of Sister Chromatid Cohesion	Reactome	10 / 126	2.04e ⁻⁰⁶	2.52e ⁻⁰⁴
Genes up-regulated by STAT5 in response to IL2 stimulation	Hallmark	12 / 199	3.61e ⁻⁰⁶	4.27e ⁻⁰⁴
Regulation of TP53 Activity through Phosphorylation	Reactome	8 / 92	1.10e ⁻⁰⁵	1.07e ⁻⁰³
MHC class II antigen presentation	Reactome	9 / 126	1.56e ⁻⁰⁵	1.36e ⁻⁰³
Network map of SARS CoV 2 signaling pathway	Wikipathways	11 / 218	4.76e ⁻⁰⁵	3.08e ⁻⁰³
Wnt signaling	Wikipathways	8 / 113	4.91e ⁻⁰⁵	3.11e ⁻⁰³
Cellular responses to stimuli	Reactome	23 / 826	9.76e ⁻⁰⁵	5.37e ⁻⁰³
Increased pathways in patients without linezolid-associated neuropathies				
Signaling by Receptor Tyrosine Kinases	Reactome	26 / 524	3.43e ⁻¹⁰	9.33e ⁻⁰⁷
MAPK signaling pathway	Wikipathways	14 / 247	8.82e ⁻⁰⁷	3.01e ⁻⁰⁴
MAPK signaling pathway	KEGG	13 / 267	1.12e ⁻⁰⁵	1.69e ⁻⁰³
Innate Immune System	Reactome	30 / 1125	1.24e ⁻⁰⁵	1.78e ⁻⁰³
Metabolism of lipids	Reactome	23 / 746	1.42e ⁻⁰⁵	1.83e ⁻⁰³
Neuroinflammation and glutamatergic signaling	Wikipathways	9 / 140	2.96e ⁻⁰⁵	3.35e ⁻⁰³
PI3K Akt signaling pathway	Wikipathways	13 / 339	1.30e ⁻⁰⁴	9.05e ⁻⁰³
Interleukin 1 IL 1 structural pathway	Wikipathways	5 / 47	1.75e ⁻⁰⁴	1.08e ⁻⁰²
Genes down-regulated in response to ultraviolet (UV) radiation	Hallmark	8 / 144	2.25e ⁻⁰⁴	1.30e ⁻⁰²
DNA damage response only ATM dependent	Wikipathways	7 / 110	2.42e ⁻⁰⁴	1.37e ⁻⁰²

Supplementary Table 2. Selected Differentially Expressed Genes. Log₂ Fold Change (log₂FC) Indicate Gene Expression of Patients with Linezolid-Associated Neuropathy Compared to Patients Without Linezolid-Associated Neuropathy

Gene	Gene Name	Log ₂ FC	P-value	Associated Pathways
BAX	BCL2 associated X, apoptosis regulator	-0.11	0.023	Mitochondrial Dysfunction
CASP3	caspase 3	0.20	0.050	Mitochondrial Dysfunction
CYCS	cytochrome c, somatic	0.13	0.028	Mitochondrial Dysfunction
GPX3	glutathione peroxidase 3	0.05	0.040	Mitochondrial Dysfunction
GPX7	glutathione peroxidase 7	0.17	0.027	Mitochondrial Dysfunction
MAPK9	mitogen-activated protein kinase 9	-0.09	0.043	Mitochondrial Dysfunction
MGST2	microsomal glutathione S-transferase 2	-0.15	0.047	Mitochondrial Dysfunction
NRF1	nuclear respiratory factor 1	0.09	0.018	Mitochondrial Dysfunction
PPP3CB	protein phosphatase 3 catalytic subunit beta	0.16	0.047	Mitochondrial Dysfunction
CEBPB	CCAAT enhancer binding protein beta	0.27	0.025	NAD Signaling Pathway
IGF1	insulin like growth factor 1	-0.05	0.033	NAD Signaling Pathway
NADSYN1	NAD synthetase 1	0.18	0.015	NAD Signaling Pathway
NMRK2	nicotinamide riboside kinase 2	0.04	0.002	NAD Signaling Pathway
PIK3R3	phosphoinositide-3-kinase regulatory subunit 3	0.05	0.025	NAD Signaling Pathway
CCNA2	Cyclin A2	0.08	0.036	DNA Damage/Telomere Stress Induced Senescence
CDKN1B	Cyclin Dependent Kinase Inhibitor 1B	0.22	0.026	DNA Damage/Telomere Stress Induced Senescence
BAX	BCL2 associated X, apoptosis regulator	-0.11	0.023	DNA Damage Response only ATM Dependent
MAPK9	mitogen-activated protein kinase 9	-0.09	0.043	DNA Damage Response only ATM Dependent
PIK3R3	Phosphoinositide-3-Kinase Regulatory Subunit 3	0.05	0.025	DNA Damage Response only ATM Dependent
WNT1	Wnt Family Member 1	0.03	0.014	DNA Damage Response only ATM Dependent
AURKB	aurora kinase B	0.05	0.047	
CDK1	cyclin dependent kinase 1 [tyrosine 3-	0.10	0.036	
YWHAE	monooxygenase/tryptophan 5-monooxygenase activation protein epsilon	-0.10	0.045	
AGT	Angiotensinogen	-0.02	0.044	Cachexia Signaling Pathway
CASP10	Caspase 10	-0.17	0.024	Cachexia Signaling Pathway
CASP3	Caspase 3	0.20	0.050	Cachexia Signaling Pathway
CASP8	Caspase 8	0.24	0.044	Cachexia Signaling Pathway
IGF1	Insulin Like Growth Factor 1	-0.05	0.033	Cachexia Signaling Pathway
IL2	Interleukin 2	0.03	0.050	Cachexia Signaling Pathway
MAP2K4	Mitogen-Activated Protein Kinase Kinase 4	-0.29	0.011	Cachexia Signaling Pathway
MAPK9	Mitogen-Activated Protein Kinase 9	-0.09	0.043	Cachexia Signaling Pathway
TNFSF15	TNF Superfamily Member 15	-0.03	0.019	Cachexia Signaling Pathway
CBR1	Carbonyl Reductase 1	-0.23	0.036	NRF2-mediated Oxidative Stress Response
HSPB8	heat shock protein family B (small) member 8	-0.03	0.047	NRF2-mediated Oxidative Stress Response

MAP2K4	Mitogen-Activated Protein Kinase Kinase 4	-0.29	0.011	NRF2-mediated Oxidative Stress Response
MAPK9	Mitogen-Activated Protein Kinase 9	-0.09	0.043	NRF2-mediated Oxidative Stress Response
MGST2	microsomal glutathione S-transferase 2	-0.15	0.047	NRF2-mediated Oxidative Stress Response
PIK3C2G	Phosphatidylinositol-4-Phosphate 3-Kinase Catalytic Subunit Type 2 Gamma	-0.03	0.003	NRF2-mediated Oxidative Stress Response
PIK3R3	Phosphoinositide-3-Kinase Regulatory Subunit 3	0.05	0.025	NRF2-mediated Oxidative Stress Response

Supplementary Table 3. Sensitivity and Specificity and Corresponding 95% Confidence Interval (95%CI) with Changing Cut-off Values for the Classification Based on the Prediction Value for Linezolid-Associated Neuropathies Using the Biomarker Algorithm.

Cut-off Value	Sensitivity (95%CI)	Specificity (95%CI)	Positive Predictive Value (95%CI)	Negative Predictive Value (95%CI)
0.1	80.0% (44.4% – 97.5%)	37.5% (21.1% – 56.3%)	28.6% (13.2% – 48.7%)	85.7% (57.2% – 98.2%)
0.2	60.0% (26.2% – 87.8%)	50.0% (31.9% – 68.1%)	27.3% (10.7% – 50.2%)	80.0% (56.3% – 94.2%)
0.3	60.0% (26.2% – 87.8%)	53.1% (34.7% – 70.9%)	28.8% (11.3% – 52.2%)	80.9% (58.1% – 94.6%)
0.4	60.0% (26.2% – 87.8%)	65.6% (46.8% – 81.4%)	35.3% (14.2% – 61.7%)	84.0% (63.9% – 95.5%)
0.5	60.0% (26.2% – 87.8%)	65.6% (46.8% – 81.4%)	35.3% (14.2% – 61.7%)	84.0% (63.9% – 95.5%)
0.6	60.0% (26.2% – 87.8%)	65.6% (46.8% – 81.4%)	35.3% (14.2% – 61.7%)	84.0% (63.9% – 95.5%)
0.7	50.0% (18.7% – 81.3%)	71.9% (53.3% – 86.3%)	35.7% (12.8% – 64.9%)	82.1% (63.1% – 93.9%)
0.8	50.0% (18.7% – 81.3%)	81.3% (63.6% – 92.8%)	45.5% (16.7% – 76.6%)	83.9% (66.3% – 94.5%)
0.9	40.0% (12.2% – 73.8%)	84.4% (67.2% – 94.7%)	44.4% (13.7% – 78.8%)	81.8% (64.5% – 93.0%)