

Online Resource 1 - Supplementary Material

Circulating Neurofilament Light Chain as a Biomarker of Chemotherapy-Induced Peripheral Neuropathy: A Systematic Review, Dependency-Robust Meta-Analysis, and Multi-Omics Evidence Integration

Supportive Care in Cancer

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Supplementary Table S1. Complete electronic search strategies

Database	Search strategy
PubMed/MEDLINE	("Neurofilament Proteins"[MeSH Terms] OR "neurofilament light chain"[Title/Abstract] OR "neurofilament light"[Title/Abstract] OR "neurofilament-light"[Title/Abstract] OR "neurofilament-L"[Title/Abstract] OR "NF-L"[Title/Abstract] OR NfL[Title/Abstract] OR NFL[Title/Abstract]) AND ("Antineoplastic Agents"[MeSH Terms] OR chemotherap*[Title/Abstract] OR antineoplastic*[Title/Abstract] OR anticancer[Title/Abstract] OR cytotoxic*[Title/Abstract] OR paclitaxel[Title/Abstract] OR docetaxel[Title/Abstract] OR taxane*[Title/Abstract] OR oxaliplatin[Title/Abstract] OR cisplatin[Title/Abstract] OR carboplatin[Title/Abstract] OR platinum*[Title/Abstract] OR vincristine[Title/Abstract] OR vinblastine[Title/Abstract] OR bortezomib[Title/Abstract] OR brentuximab[Title/Abstract]) AND ("Peripheral Nervous System Diseases"[MeSH Terms] OR neuropath*[Title/Abstract] OR polyneuropath*[Title/Abstract] OR neurotox*[Title/Abstract] OR axon*[Title/Abstract] OR "nerve conduction"[Title/Abstract] OR CIPN[Title/Abstract] OR PIPN[Title/Abstract] OR OIPN[Title/Abstract] OR VIPN[Title/Abstract] OR BIPN[Title/Abstract])
Embase	('neurofilament light chain':ti,ab,kw OR 'neurofilament light':ti,ab,kw OR 'neurofilament-light':ti,ab,kw OR 'neurofilament-l':ti,ab,kw OR 'nf-l':ti,ab,kw OR nfl:ti,ab,kw) AND (chemotherap*:ti,ab,kw OR antineoplastic*:ti,ab,kw OR anticancer:ti,ab,kw OR cytotoxic*:ti,ab,kw OR paclitaxel:ti,ab,kw OR docetaxel:ti,ab,kw OR taxane*:ti,ab,kw OR oxaliplatin:ti,ab,kw OR cisplatin:ti,ab,kw OR carboplatin:ti,ab,kw OR platinum*:ti,ab,kw OR vincristine:ti,ab,kw OR vinblastine:ti,ab,kw OR bortezomib:ti,ab,kw OR brentuximab:ti,ab,kw) AND (neuropath*:ti,ab,kw OR polyneuropath*:ti,ab,kw OR neurotox*:ti,ab,kw OR axon*:ti,ab,kw OR 'nerve conduction':ti,ab,kw OR cipn:ti,ab,kw OR pipn:ti,ab,kw OR oipn:ti,ab,kw OR vipn:ti,ab,kw OR bipn:ti,ab,kw)
Web of Science Core Collection	TS=(("neurofilament light chain" OR "neurofilament light" OR "neurofilament-light" OR "neurofilament-L" OR "NF-L" OR NfL OR NFL) AND (chemotherap* OR antineoplastic* OR anticancer OR cytotoxic* OR paclitaxel OR docetaxel OR taxane* OR oxaliplatin OR cisplatin OR carboplatin OR platinum* OR vincristine OR vinblastine OR bortezomib OR brentuximab) AND (neuropath* OR polyneuropath* OR neurotox* OR axon* OR "nerve conduction" OR CIPN OR PIPN OR OIPN OR VIPN OR BIPN))
Cochrane CENTRAL	("neurofilament light chain" OR "neurofilament light" OR "neurofilament-light" OR "neurofilament-L" OR "NF-L" OR NfL OR NFL) AND (chemotherap* OR antineoplastic* OR anticancer OR cytotoxic* OR paclitaxel OR docetaxel OR taxane* OR oxaliplatin OR cisplatin OR carboplatin OR platinum* OR vincristine OR vinblastine OR bortezomib OR brentuximab) AND (neuropath* OR polyneuropath* OR neurotox* OR axon* OR "nerve conduction" OR CIPN OR PIPN OR OIPN OR VIPN OR BIPN); fields: title/abstract/keywords

Supplementary Table S2. Study-level effect sizes used in the final correlation meta-analyses

Analysis	Study	n	Outcome	Reported type	Direction-harmonized r	95% CI for r
Clinical severity	Huehnchen 2022	30	Δ sNfL vs Δ TNSr	Spearman r	0.510	0.183–0.735
Clinical severity	Kim 2020	34	6-month sNfL vs total CIPN20	Pearson r	0.565	0.280–0.758
Clinical severity	Kim 2022	48	Post-cycle-6 sNfL vs CIPN20 sensory subscale	Partial correlation	0.389	0.118–0.606
Clinical severity	Velasco 2023	27	sNfL vs TNSc	Pearson r	0.397	0.020–0.675
Clinical severity	Gehr 2025	9	Δ NfL vs OIPN symptoms	Spearman r	0.810	0.316–0.959
Clinical severity	Smyth 2026	30	sNfL z-score vs CIPN-RODS	Spearman r	0.450	0.107–0.697
Clinical severity	Stephan 2025	56	Δ NfL vs Δ TNSr	Pearson r	0.385	0.136–0.588
Objective nerve injury	Kim 2020	34	sNfL vs sural SNAP amplitude	Pearson r	0.410	0.083–0.657
Objective nerve injury	Kim 2022	48	sNfL vs sural sensory conduction velocity	Partial correlation	0.361	0.086–0.585
Objective nerve injury	Cebulla 2023	33	sNfL vs sural SNAP amplitude	Spearman r	0.380	0.042–0.640
Objective nerve injury	Velasco 2023	22	sNfL vs axonal loss on NCS	Pearson r	0.620	0.269–0.826
Objective nerve injury	Tikhonova 2026	51	sNfL vs IENFD	Spearman r	0.416	0.159–0.620

Supplementary Table S3. Reported diagnostic and prognostic performance metrics

Study [reference]	NfL time point	Target outcome	Threshold	Sensitivity	Specificity	AUC (95% CI)	Other estimate
Kim 2020 [9]	6 months	Grade 3 OIPN	195 pg/mL	0.80	0.862	NR	—
Kim 2022 [10]	After 2 cycles	Final grade 3 PIPN	124 pg/mL	0.80	0.79	NR	—
Kim 2022 [10]	After 6 cycles	Grade 3 PIPN	250 pg/mL	0.90	0.89	NR	—
Burgess 2022 [11]	Day-21 change	Subsequent grade 2–3 CIPN	73.4 pg/mL	NR	NR	0.76 (0.65–0.86)	PPV 0.68; NPV 0.66
Burgess 2022 [11]	Day-21 change	Unresolved grade 2–3 CIPN	88 pg/mL	NR	NR	0.81 (0.72–0.90)	PPV 0.67; NPV 0.67
Huehnchen 2022 [12]	Post-chemotherapy change	Clinically relevant CIPN	+7.05 pg/mL	0.86	0.87	NR	—
Karteri 2022 [13]	Week 3	Grade 2–3 PIPN at week 12	>85 pg/mL	0.462	0.848	0.63 (0.47–0.78)	Adjusted OR 5.65 (1.45–21.74)
Mortensen 2023 [14]	After cycle 1	Paclitaxel discontinuation due to PIPN	>150 vs <50 pg/mL	NR	NR	NR	Adjusted HR 2.25 (0.88–5.79)
Makówka 2025 [21]	During treatment	Early neuropathy	29.5 pg/mL	NR	NR	0.982 (CI NR)	—
Tikhonova 2026 [26]	Post-chemotherapy	Prediction of CIPN	95.37 pg/mL	0.909	0.357	0.526 (0.321–0.731)	No predictive value

Supplementary Table S4. Principal results of multi-omics evidence integration

Analysis layer	Metric	Result	Interpretation
Transcriptomics	Shared genes	19,605	Two complete 48-h PTX contrasts
Transcriptomics	FDR < 0.05	3,289	Multiple-testing correction among shared genes
Transcriptomics	Significant and directionally concordant	3,115	Agreement between two primary datasets
GSE173610 verification	Directionally concordant significant genes	363/364	Directional verification only
Three-dataset sensitivity	FDR < 0.05	412/585	Affected by significance filtering
Prespecified pathways	Primary-analysis FDR < 0.05	7/12	Matched DMSO3 control
Batch-robust pathway	Sterol biosynthesis	1 pathway	Remained robust using alternative DMSO2
Proteomics	RNA–protein mapped pairs	93	PXD070094 supplementary table
Proteomics	Spearman rho	0.6015	$p = 1.82 \times 10^{-10}$
Proteomics	Directional concordance	79.6%	Orthogonal consistency, not causal mediation

Supplementary Figure S1

QUIPS risk-of-bias traffic light
23 assessed reports; L=Low, M=Moderate, H=High

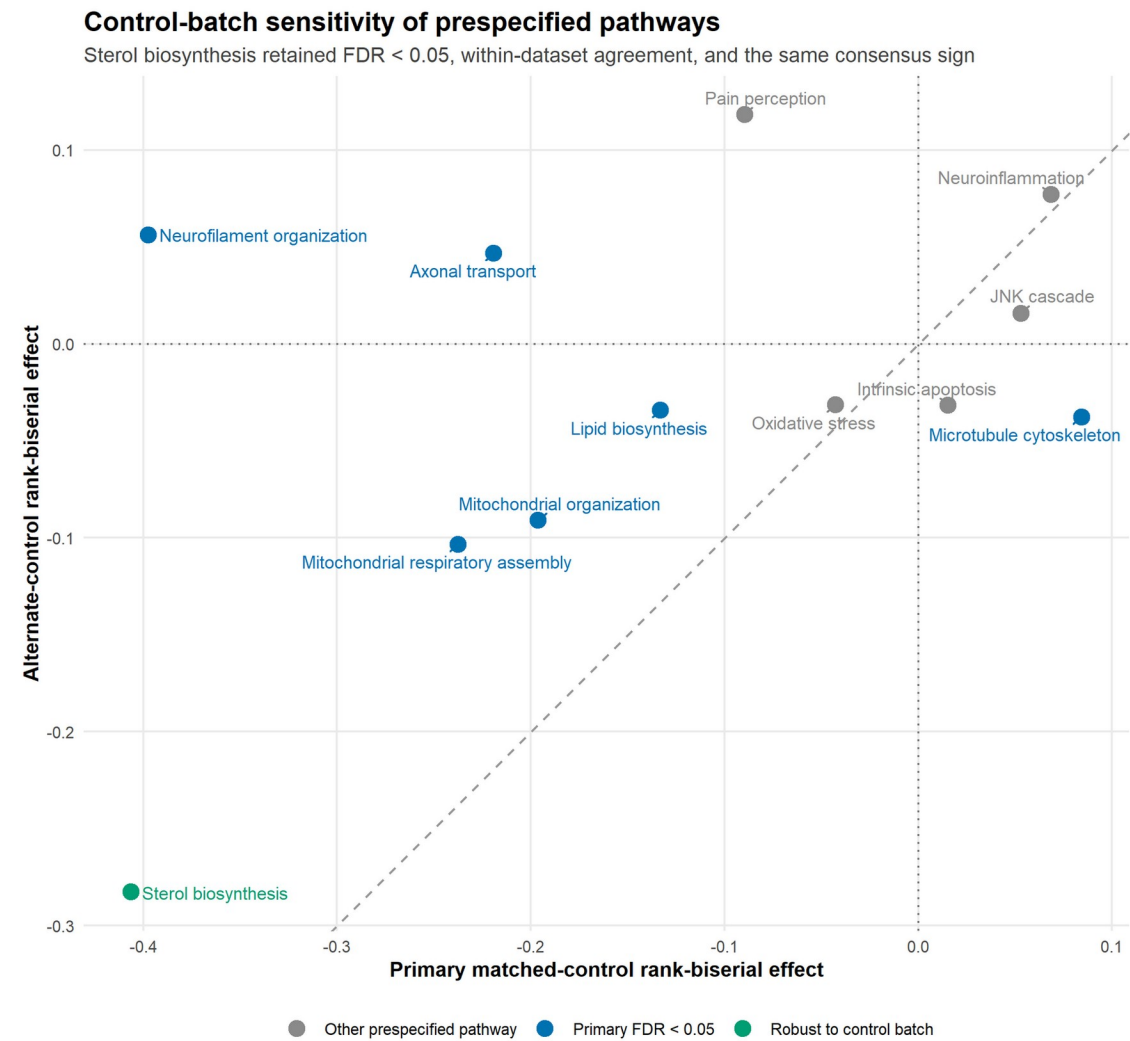
Kim 2020	L	M	L	L	M	L
Kim 2022	L	M	L	L	L	M
Burgess 2022	L	M	L	M	L	M
Huehnchen 2022	L	L	L	L	M	L
Karteri 2022	L	L	L	L	L	M
Mortensen 2023	M	L	L	M	M	M
Cebulla 2023	M	L	L	L	M	M
Velasco 2023	M	M	L	L	L	L
Cavaletti 2023	L	M	L	M	M	M
Adra 2024	M	M	L	L	M	M
Velasco 2024	L	M	L	L	M	M
Gehr 2025	M	H	M	H	M	M
Kittaka 2026	M	M	L	M	M	M
Pontoppidan 2026	M	L	L	M	L	M
Smyth 2026	L	M	L	L	L	L
Makówka 2025	L	M	L	L	M	L
Stephan 2025	L	M	L	M	L	L
Tikhonova 2026	M	M	L	M	L	L
Beales 2026	L	M	L	L	M	L
Tantawy 2025	L	L	M	L	M	M
Velasco 2026	M	H	L	L	M	M
Kassem 2025	M	L	M	M	H	H
Belsky 2026	M	M	L	L	M	M

D1 Participation D2 Attrition D3 PF measurement D4 Outcome D5 Confounding D6 Analysis/reporting

Risk level ■ Low ■ Moderate ■ High

Supplementary Fig. S1 Study-level QUIPS judgments for 23 reports. Rows represent reports and columns represent QUIPS domains; colors and letters indicate low, moderate, and high risk

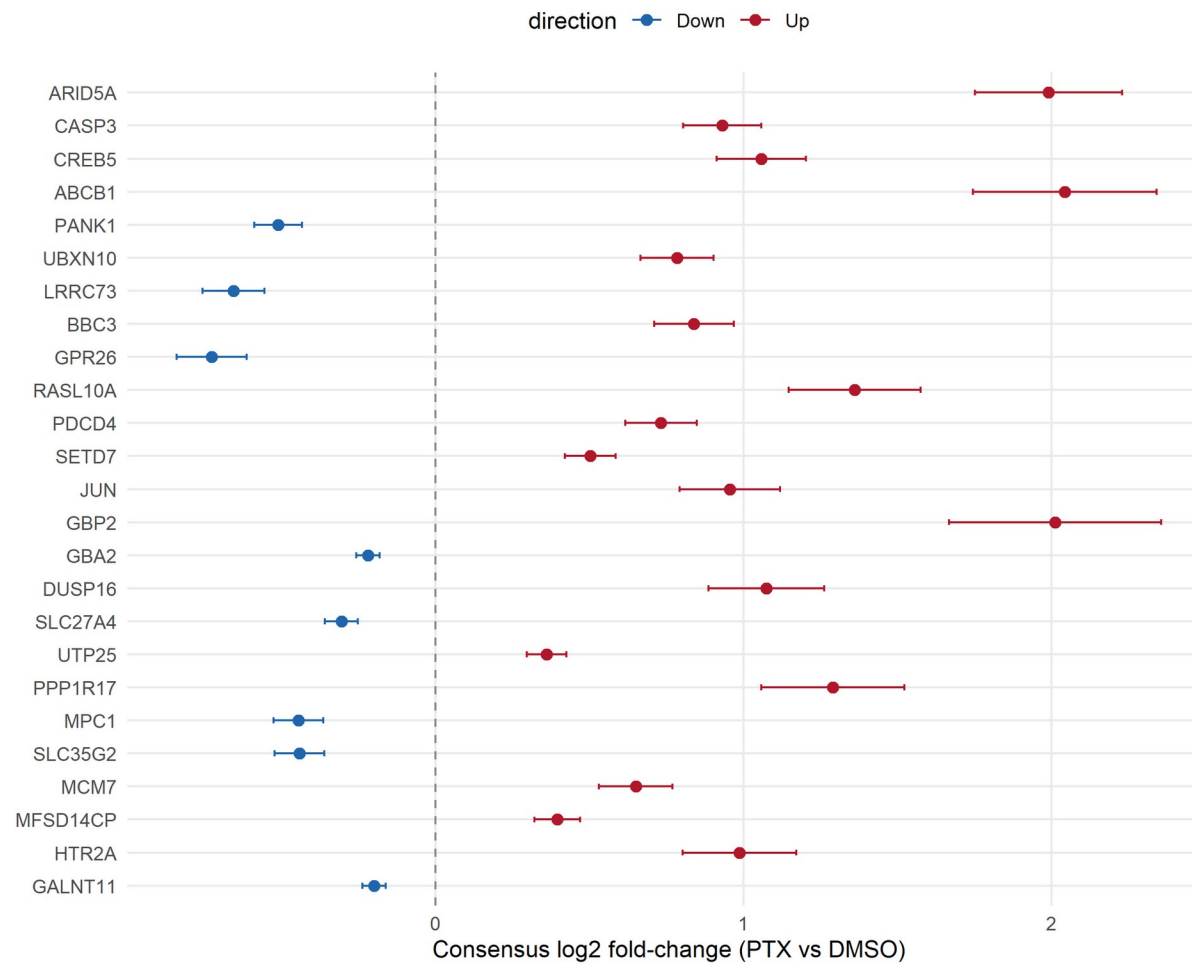
Supplementary Figure S2



Supplementary Fig. S2 Comparison of pathway effects using matched and alternative control batches. Sterol biosynthesis met all prespecified robustness criteria

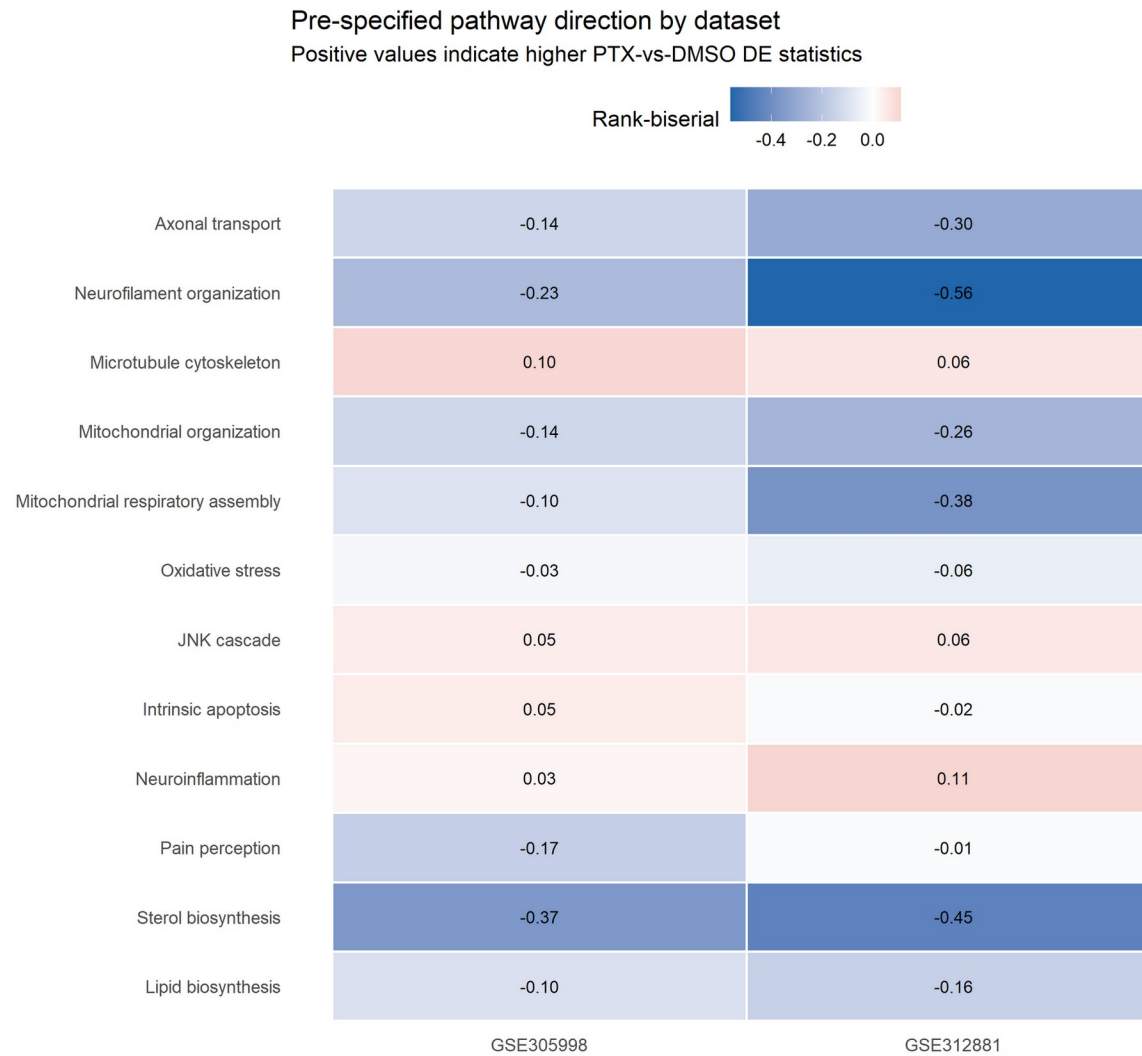
Supplementary Figure S3

Cross-dataset transcriptomic consensus Two complete 48-h datasets; random-effects REML



Supplementary Fig. S3 Consensus genes with the most prominent cross-dataset effects in two complete 48-h paclitaxel-control datasets

Supplementary Figure S4

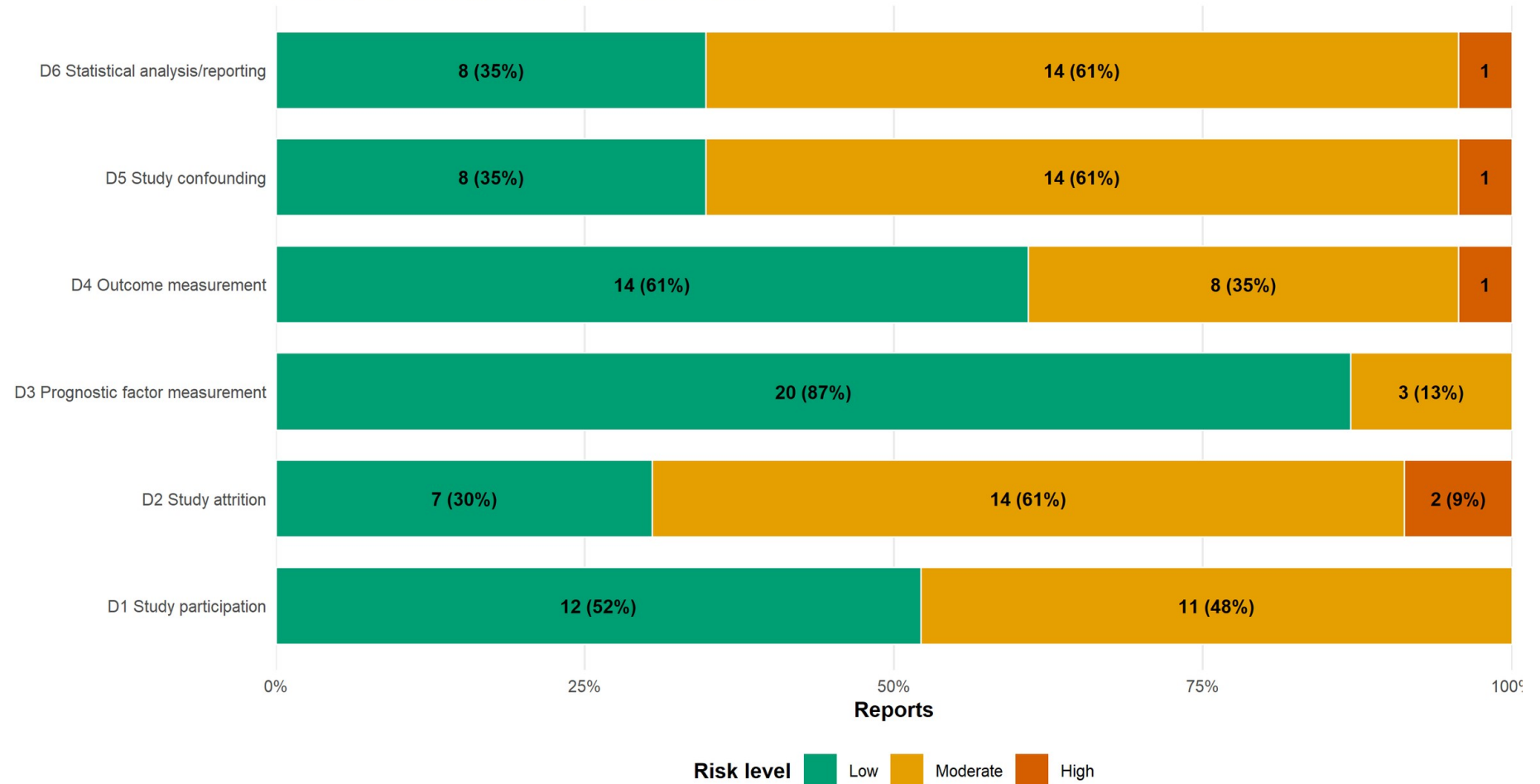


Supplementary Fig. S4 Direction and significance of effects for 12 prespecified pathways across the primary transcriptomic datasets

Supplementary Figure S5

QUIPS domain-level distribution

Counts and percentages across 23 assessed reports

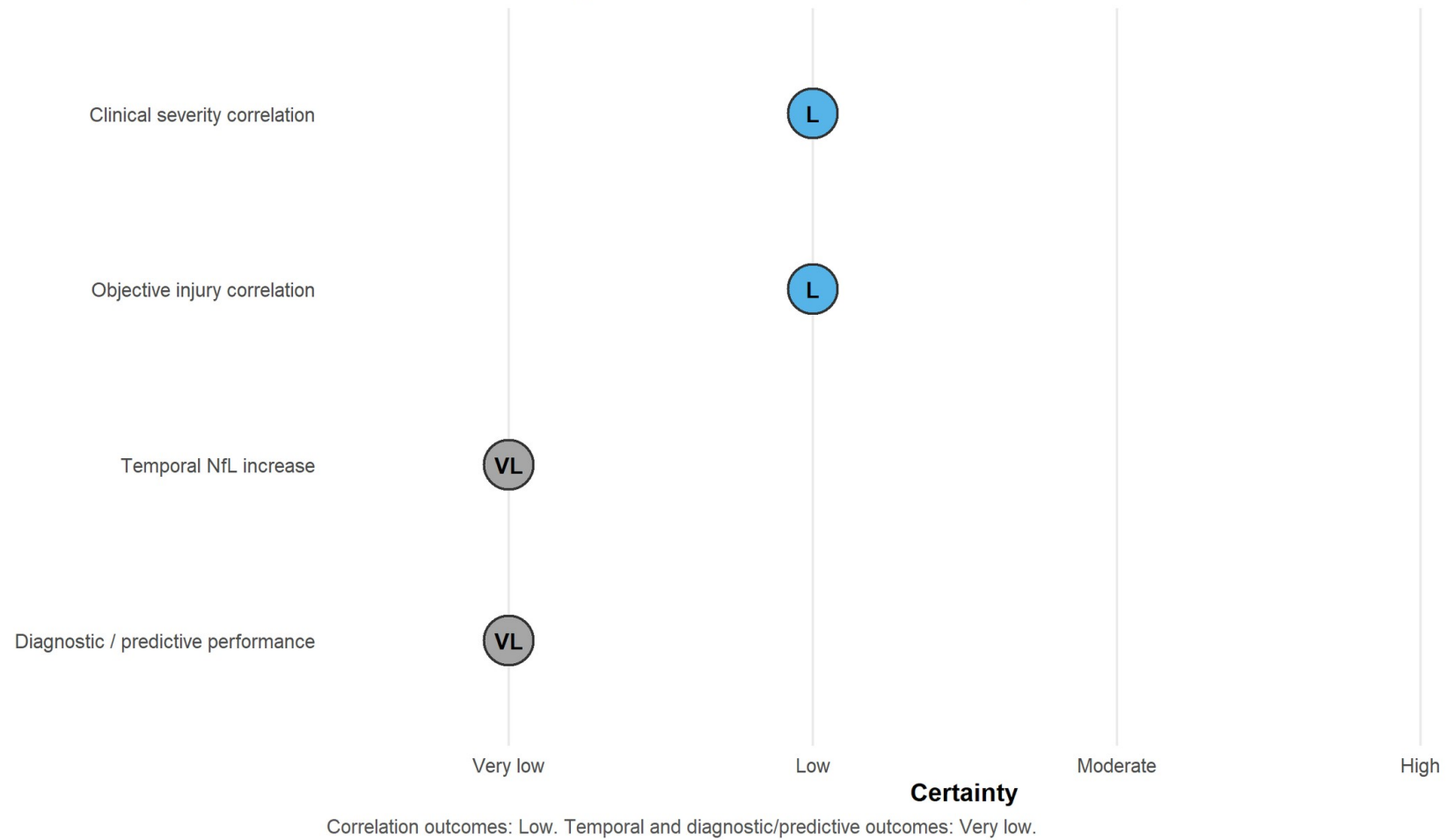


Supplementary Fig. S5 QUIPS domain-level risk distribution across 23 reports. Green, yellow, and orange-red indicate low, moderate, and high risk, respectively

Supplementary Figure S6

GRADE certainty overview

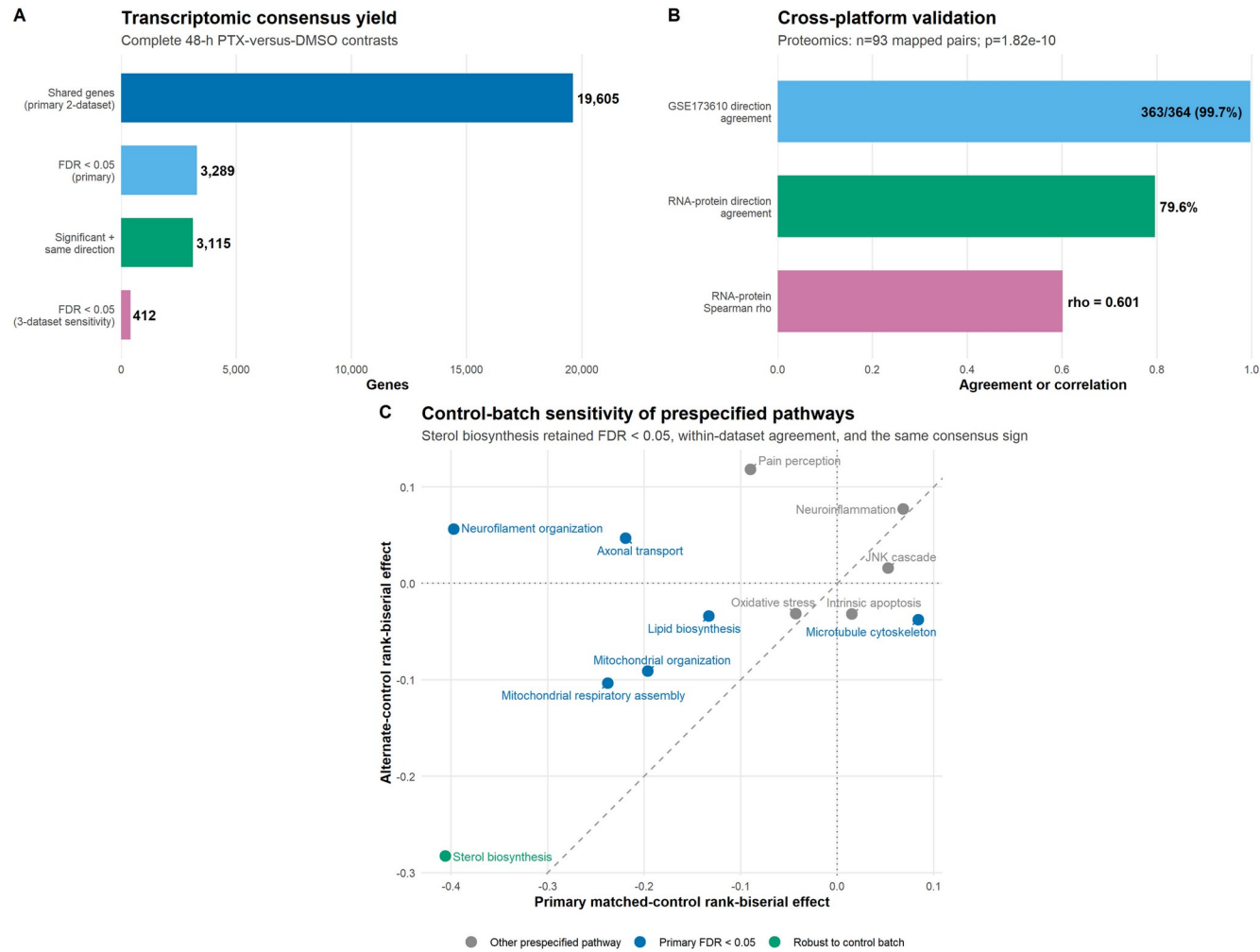
Outcome-level certainty after the final available-evidence analysis



Supplementary Fig. S6 GRADE certainty of evidence for the principal outcome domains

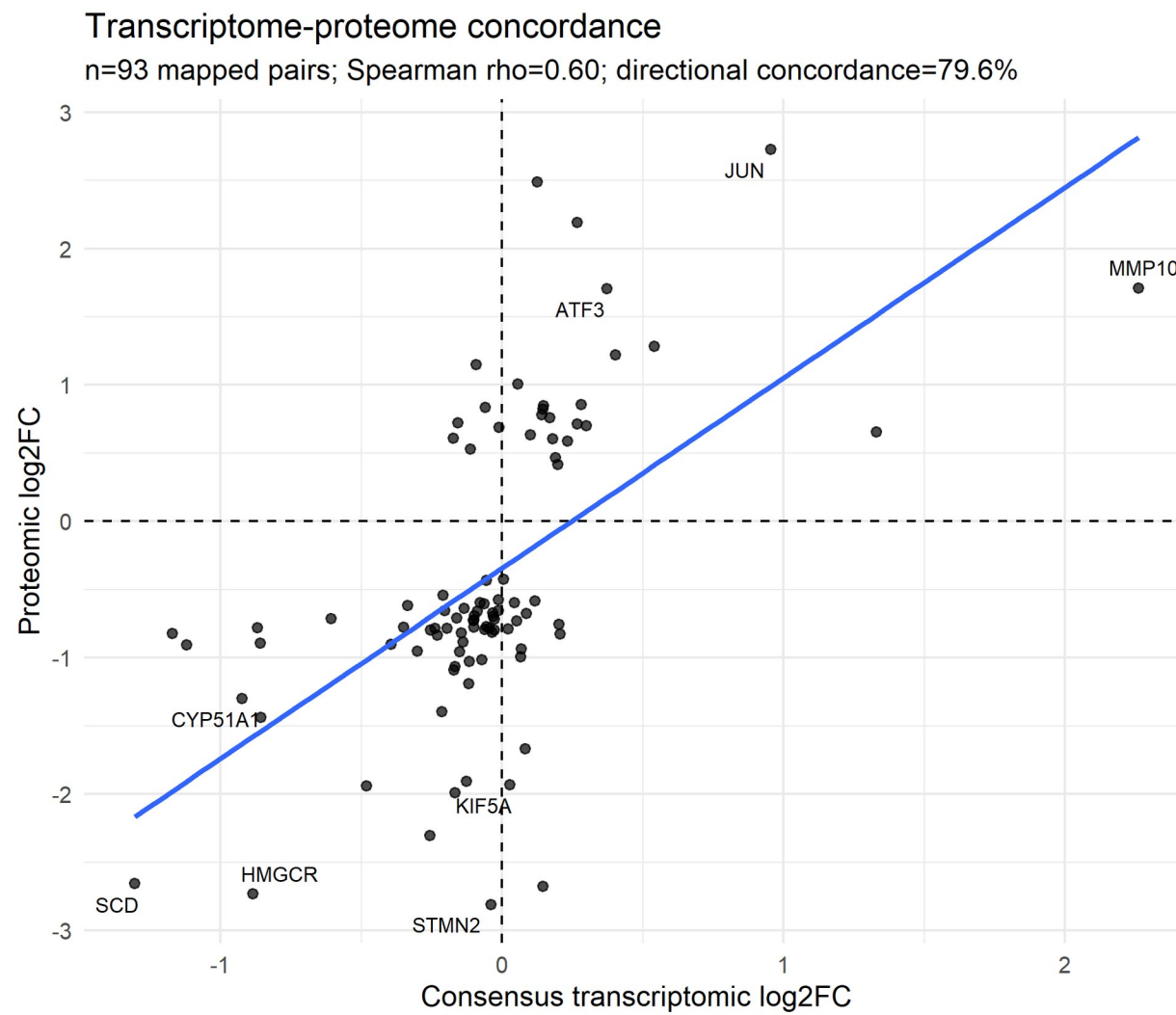
Supplementary Figure S7

Integrated multi-omics evidence overview



Supplementary Fig. S7 Multi-omics overview of transcriptomic consensus, cross-platform validation, and control-batch sensitivity of prespecified pathways

Supplementary Figure S8



Supplementary Fig. S8 Cross-omics concordance of effect estimates for 93 mapped RNA-protein pairs