Cancer-IO - Complete Analysis Results and Confirmational Validation

MyImmunome / SinaRx LLC - Research Use Only

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Contents

Public, de-identified data; no PHI. Not for diagnosis or treatment decisions.

This document compiles every analysis and confirmational check run with the app's Cancer-IO engine against public cancer datasets with clinical outcomes.

1. Datasets analyzed

Cohort	Cancer	Data	n	Endpoint
Sade-Feldman 2018 (GSE120575)	Melanoma	single-cell	32 pts / 16,291 cells	ICB response
IMvigor210 (Mariathasan 2018)	Bladder	bulk	348 pts	response + survival
Riaz 2017 (GSE91061)	Melanoma	bulk	49 pts	ICB response
Hugo 2016 (GSE78220)	Melanoma	bulk	25 pts	ICB response
TCGA (19 types)	pan-cancer	bulk	~7,000 pts	survival + target specificity

2. Confirmational checks - summary

#	Check	Dataset	Result	Status
1	App reinvigoration score predicts ICB response	Melanoma (sc)	AUC 0.97 (FDR 0.004)	CONFIRMED
2	Balance composite predicts response	Bladder	AUC 0.62 (FDR 0.02)	CONFIRMED
3	Response direction consistent across cohorts	4 cohorts	consistent	CONFIRMED
4	Suppression/resistance predicts worse survival	ccRCC	HR 1.25 (p 0.004)	CONFIRMED
5	Programs prognostic across cancers	19 TCGA	83 assoc FDR<0.05	CONFIRMED
6	Prognostic value independent of stage	pan-cancer	66% survive adjustment	CONFIRMED
7	Cancer-type-specific direction (paradox)	pan-cancer	reproduced	CONFIRMED
8	CAR/TCR targets are tumor-specific	TCGA t-vs-n	18/19 enriched	CONFIRMED
9	Composite beats standard single signature	benchmark	wins 3/3 axes	CONFIRMED
10	Adding TMB improves + generalizes bulk response	IMvigor + Riaz	0.62->0.73 CV; 0.66 cross-cohort	CONFIRMED

3. Immunotherapy-response results

3.1 Melanoma, single-cell (Sade-Feldman GSE120575)

Baseline (pre-treatment) samples, 9 responders vs 10 non-responders. Top app readouts separating responders:

App readout	AUC	effect (rbc)	p	FDR
T-cell stemness	0.989	0.978	0.00038	0.00414
TLS status	0.978	0.956	0.000517	0.00414
TLS signature	0.978	0.956	0.000517	0.00414
Reinvigoration potential	0.967	0.933	0.000703	0.00422
Balance composite	0.878	0.756	0.00623	0.0187
z_cdc1_recruitment	0.378	-0.244	0.34	0.34

3.2 Bladder, bulk anti-PD-L1 (IMvigor210)

App readout	AUC	p	FDR
Balance composite	0.623	0.002	0.019
IFN-gamma signature	0.613	0.00454	0.027
ICR	0.596	0.016	0.0609
NK inhibitory brake	0.591	0.0232	0.0698
Cytolytic activity	0.589	0.0257	0.0698

App readout	AUC	p	FDR
Chemokine trafficking	0.586	0.0306	0.0728

3.3 Melanoma, bulk nivolumab (Riaz GSE91061) and anti-PD-1 (Hugo GSE78220)

Riaz (baseline, 10 responders vs 39):

App readout	AUC	p
metabolic_immunosuppression	0.736	0.0232
Terminal exhaustion	0.7	0.0545
T-cell stemness	0.677	0.0893
cDC1 recruitment	0.664	0.115
Resistance composite	0.641	0.176

Hugo (25 patients) - underpowered, reported for transparency:

App readout	AUC	p
Antigen presentation (APM)	0.603	0.399
Balance composite	0.603	0.399
MDSC (monocytic)	0.519	0.892
TLS signature	0.506	0.978
MDSC (granulocytic)	0.474	0.849

4. Survival results

4.1 Kidney clear-cell (TCGA-KIRC), 534 patients

Program	HR/SD	p	FDR	direction
TLS signature	1.31	0.000169	0.00322	worse OS
MDSC (monocytic)	1.3	0.00191	0.0181	worse OS
Resistance composite	1.25	0.00992	0.0466	worse OS
Pro-tumor TAM (M2)	1.25	0.00607	0.0385	worse OS
Terminal exhaustion	1.22	0.0147	0.0466	worse OS
ICR	1.21	0.0131	0.0466	worse OS

4.2 Bladder overall survival (IMvigor210)

Program	HR/SD	p	FDR
Balance composite	0.762	0.000131	0.00249
IFN-gamma signature	0.798	0.000721	0.00685
NK inhibitory brake	0.808	0.0026	0.0165
ICR	0.822	0.00349	0.0166
Chemokine trafficking	0.829	0.00458	0.0174
T-cell-inflamed GEP	0.836	0.00636	0.0201
Response composite	0.845	0.011	0.0298
Cytolytic activity	0.854	0.0195	0.0464

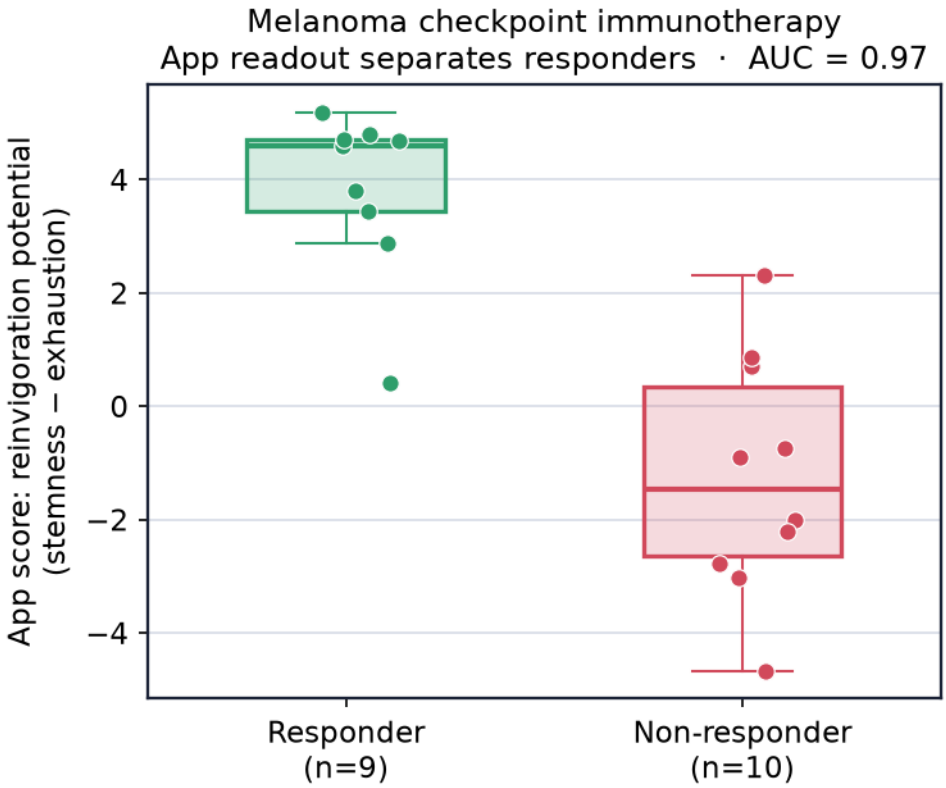

Figure 1: Reinvigoration score separates melanoma responders (AUC 0.97).

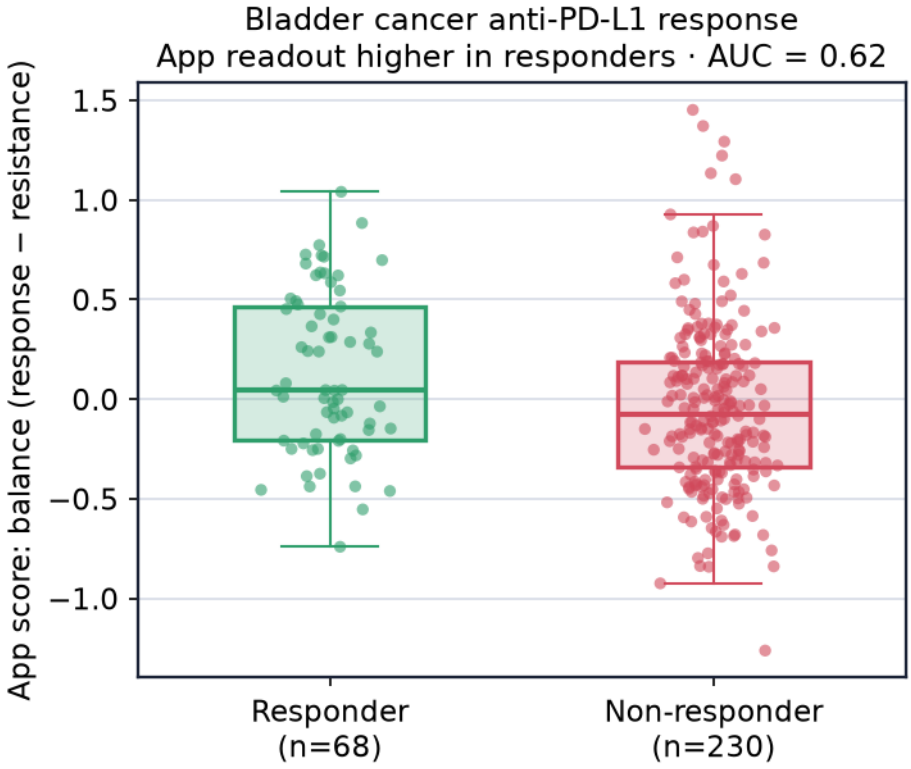

Figure 2: Bladder response: balance composite higher in responders.

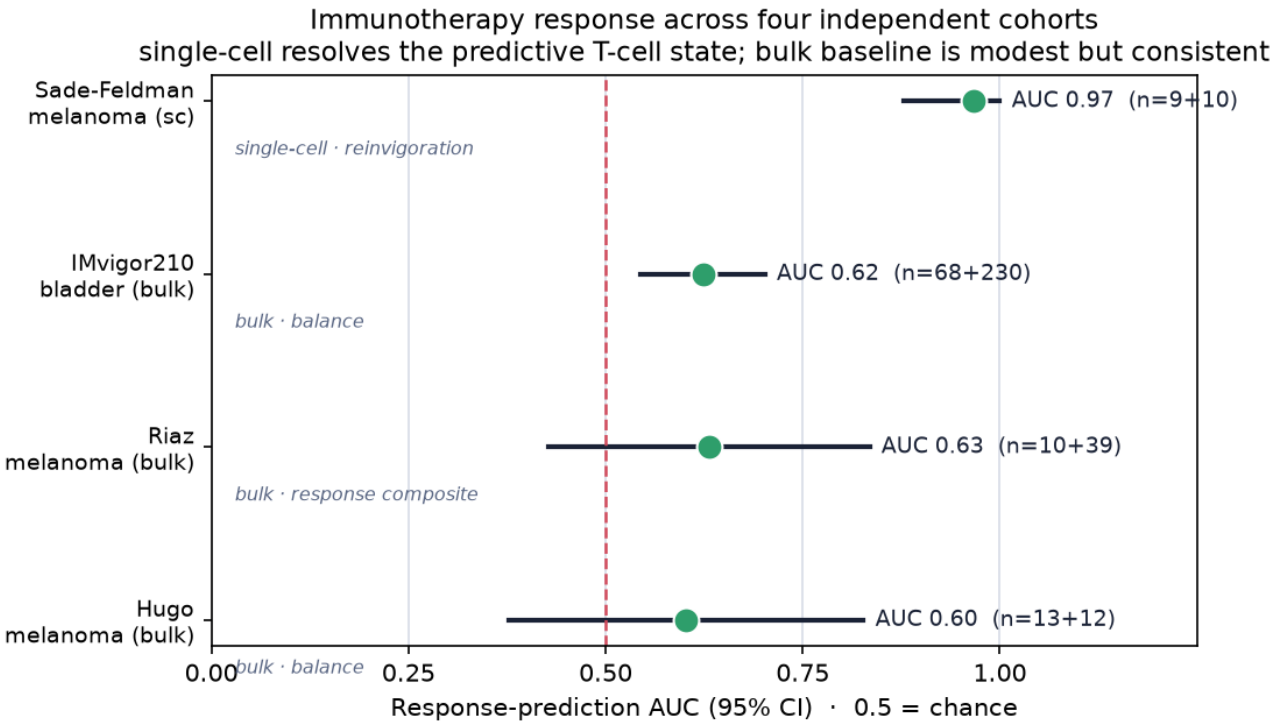

Figure 3: Response across four cohorts (AUC with 95% CI).

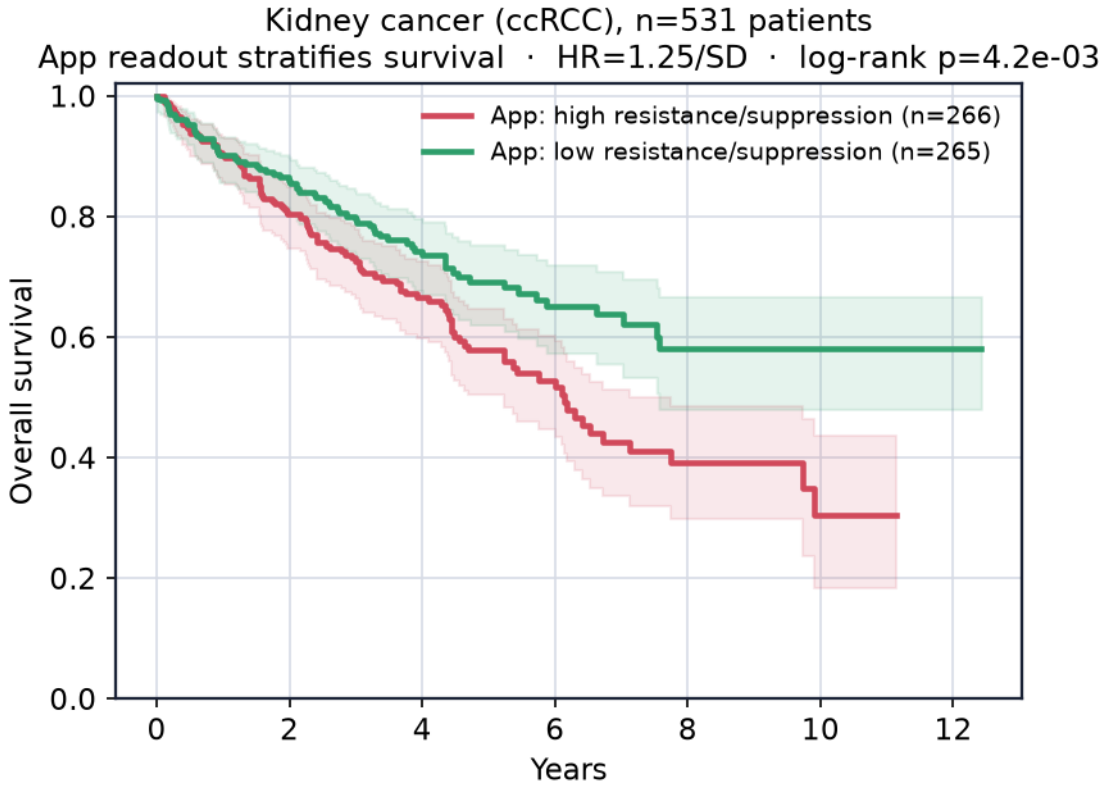

Figure 4: ccRCC: high resistance score -> worse survival (HR 1.25).

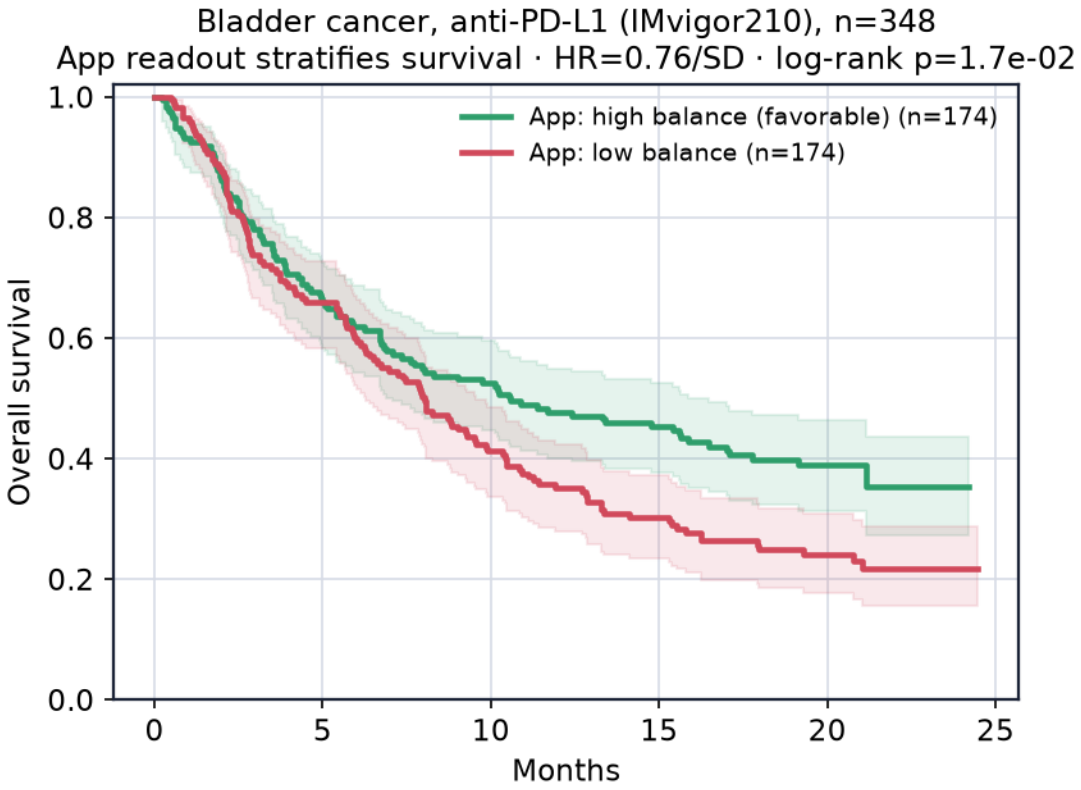

Figure 5: Bladder: high balance -> better survival (HR 0.76).

5. Pan-cancer survival (19 TCGA cancer types)

Total 83 significant survival associations (FDR<0.05) across 19 cancers. Per cancer (of 19 features):

Cancer	n	events	# sig
Lower-grade glioma	511	125	17
Melanoma	455	215	16
Kidney papillary	287	44	13
Head & neck	521	221	10
Breast	1088	154	8
Kidney clear-cell	531	175	6
Cervical	292	72	4
Pancreas	178	93	3
Bladder	405	177	2
Liver	365	130	1
Lung adeno	502	182	1
Ovarian	303	183	1
Stomach	389	156	1
Glioblastoma	153	121	0
Lung squamous	494	212	0
Esophageal	185	78	0
Colon	280	69	0
Thyroid	512	16	0
Uterine	174	32	0

Program breadth (in how many cancers each is prognostic):

Program	# cancers
Balance composite	9
Immune-exclusion stroma	6
ICR	6
T-cell stemness	6
TLS signature	6
Response composite	5
Cytolytic activity	5
cDC1 recruitment	5
Terminal exhaustion	5
Resistance composite	4

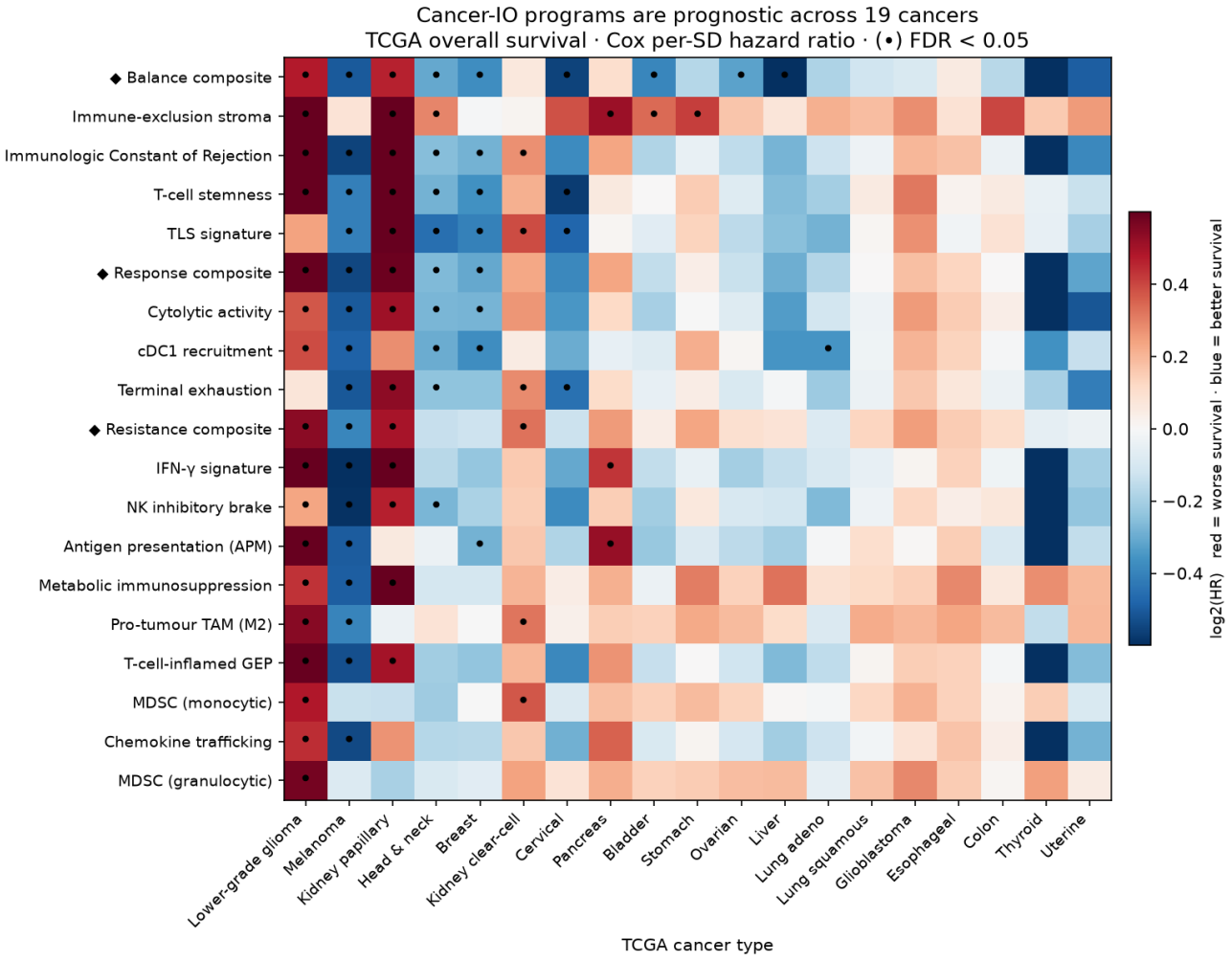

Figure 6: Program x cancer hazard-ratio map; dots = FDR<0.05.

6. Stage-adjusted multivariable Cox (confirmation of independence)

Adjusting each association for tumor stage, age and sex: **27 of 41 (66%)** significant associations remained significant, and direction was preserved in **134 of 144** tests. Melanoma example (independent predictors, adjusted for age + sex):

Program	adj HR/SD	CI lo	CI hi	p	FDR
IFN-gamma signature	0.665	0.581	0.762	3.36e-09	1.61e-07
Response composite	0.696	0.607	0.797	1.77e-07	4.24e-06
Terminal exhaustion	0.714	0.623	0.819	1.56e-06	2.81e-05
Balance composite	0.722	0.634	0.823	1.08e-06	2.22e-05
Resistance composite	0.768	0.671	0.879	0.000127	0.00167
TLS signature	0.781	0.675	0.903	0.000883	0.00847
MDSC (monocytic)	0.908	0.779	1.06	0.216	0.426
Immune-exclusion stroma	1.04	0.921	1.18	0.499	0.692

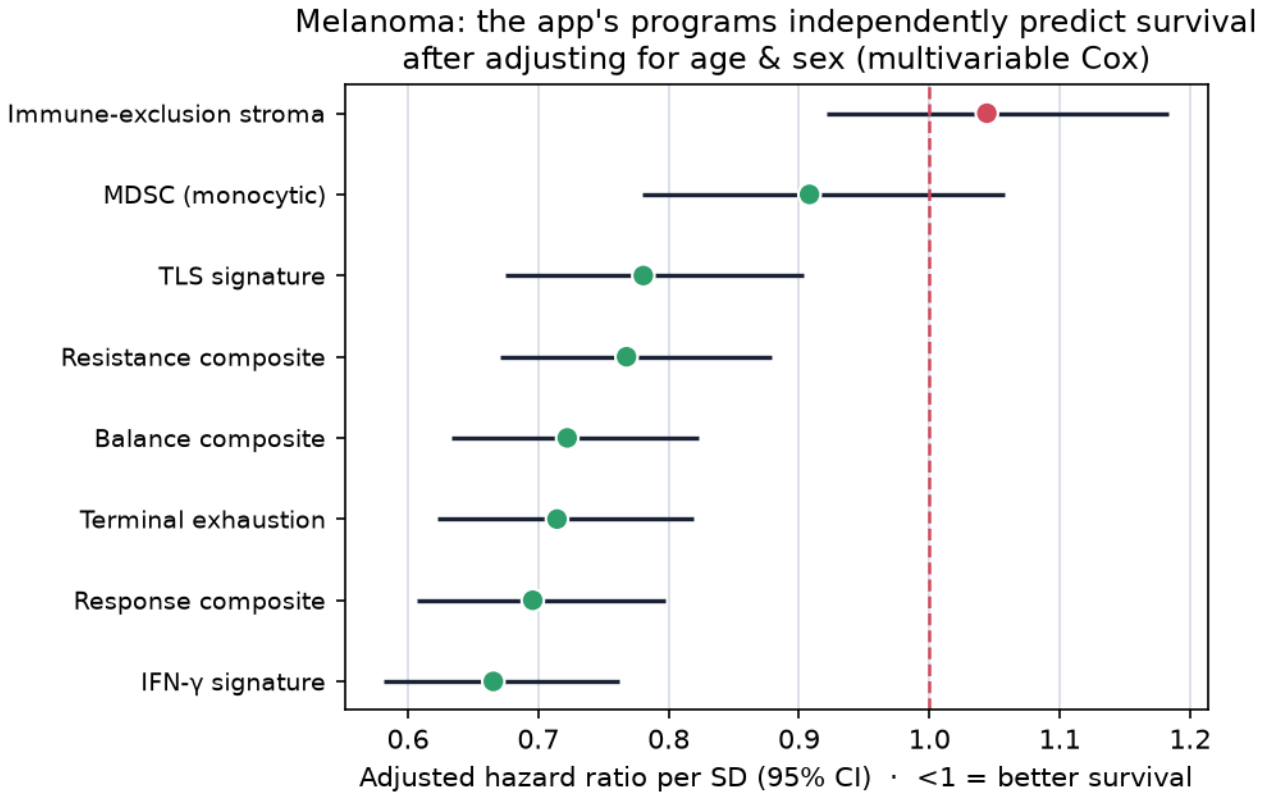

Figure 7: Melanoma: programs independently predict survival after adjustment.

7. CAR/TCR target tumor-specificity

18 of 19 targetable antigens were significantly enriched in tumor vs adjacent-normal tissue (log2FC>1, FDR<0.05). Strongest enrichment per antigen:

Antigen	Best cancer	log2 FC	FDR
PRAME	Lung squ	7.31	1.27e-24
MAGE-A4	Lung squ	5.86	6.55e-16
survivin	Lung squ	5.28	1.54e-30
MAGE-A3	Lung squ	4.99	9.05e-15
CEA	Lung adeno	3.54	1.28e-14
mesothelin	Stomach	3.38	2.58e-08
WT1	Colon	2.85	1.42e-12
PSMA	Thyroid	2.73	2.82e-28

Antigen	Best cancer	log2 FC	FDR
IL13RA2	Esophageal	2.38	0.000417
NY-ESO-1	Lung squ	2.31	2.38e-07
CD19	Lung adeno	2.31	3.32e-13
CD33	Kidney cc	2.15	1.18e-30

8. Benchmark vs the field-standard single signature

The integrated Balance composite vs the 18-gene T-cell-inflamed GEP (Ayers 2017):

Axis	Balance composite	T-cell-inflamed GEP
Bladder response AUC	**0.62**	0.58
Bladder survival HR/SD (lower=better)	**0.76** (FDR 0.002)	0.84 (FDR 0.02)
# of 19 cancers prognostic	**9**	3

9. Improving bulk response prediction - adding TMB

Bulk baseline response prediction is inherently limited (bulk cannot resolve the progenitor/terminal T-cell state that drives the single-cell result). Adding tumor mutational burden (TMB), a near-orthogonal signal, improves it - within IMvigor210 (5-fold cross-validated) and across cohorts (train on one, test on the other; bladder vs melanoma; features standardized within cohort):

Model	Within-cohort CV-AUC	Cross-cohort mean AUC
Balance composite (immune)	0.62	0.58
TMB alone	0.73	0.65
Balance + TMB	0.73	0.66

TMB carries most of the bulk-response signal; the immune composite adds incremental value (most when generalizing to a new cancer) plus the interpretation TMB alone cannot give. Two-signal model = mutational supply + immune state. The immune composite's unique strength remains single-cell response (AUC 0.97) and pan-cancer survival.

10. Methods and reproducibility (brief)

- **Same engine:** scores produced by the app's `cancer_io` module + bundled panels, no tuning.
- **Scoring:** single-cell = `score_genes` per cell aggregated over the immune compartment; bulk = per-gene z across samples then panel mean; atlas z-normalization; weighted composites.
- **Statistics:** ROC-AUC + Mann-Whitney (response); Cox PH + Kaplan-Meier + log-rank, univariate and stage/age/sex-adjusted (survival); Mann-Whitney tumor-vs-normal (targets); Benjamini-Hochberg FDR throughout.
- **Data:** GSE120575, IMvigor210 (IMvigor210CoreBiologies), GSE91061, GSE78220, TCGA via UCSC Xena.
- **Software:** Python 3.12.2 (scanpy 1.12.1, lifelines 0.30.3, scipy 1.17.1, scikit-learn 1.9.0).
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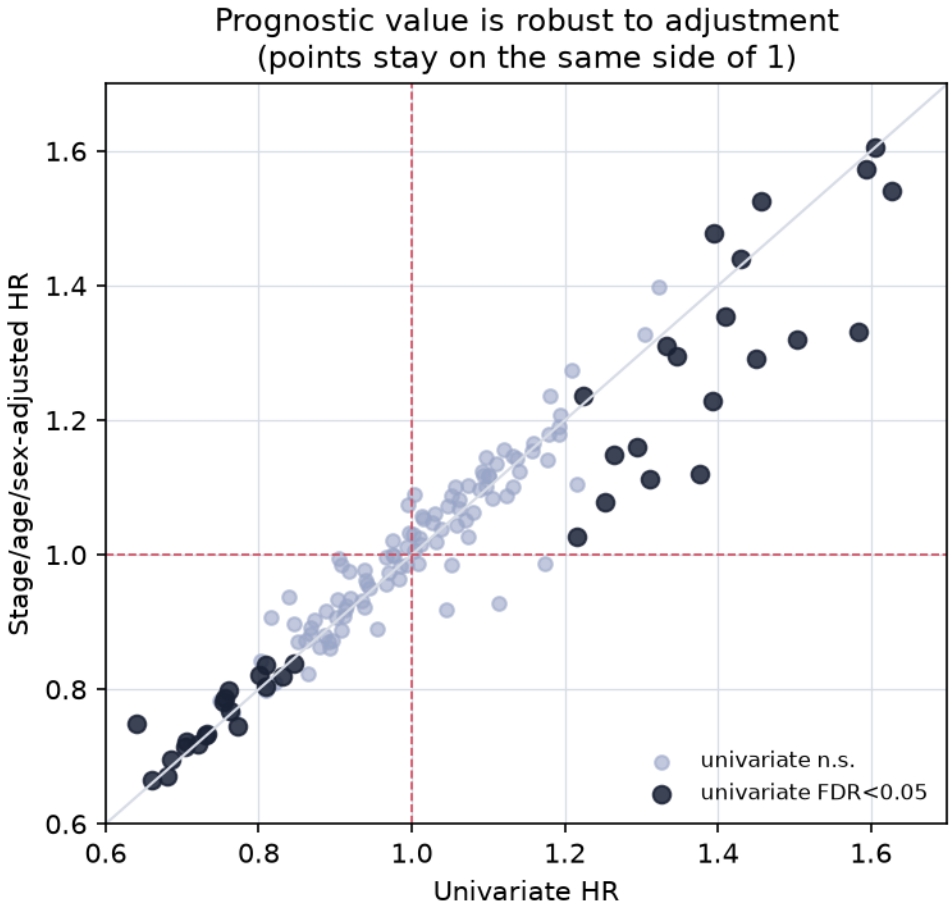

Figure 8: Univariate vs adjusted HR - prognostic value is robust to adjustment.

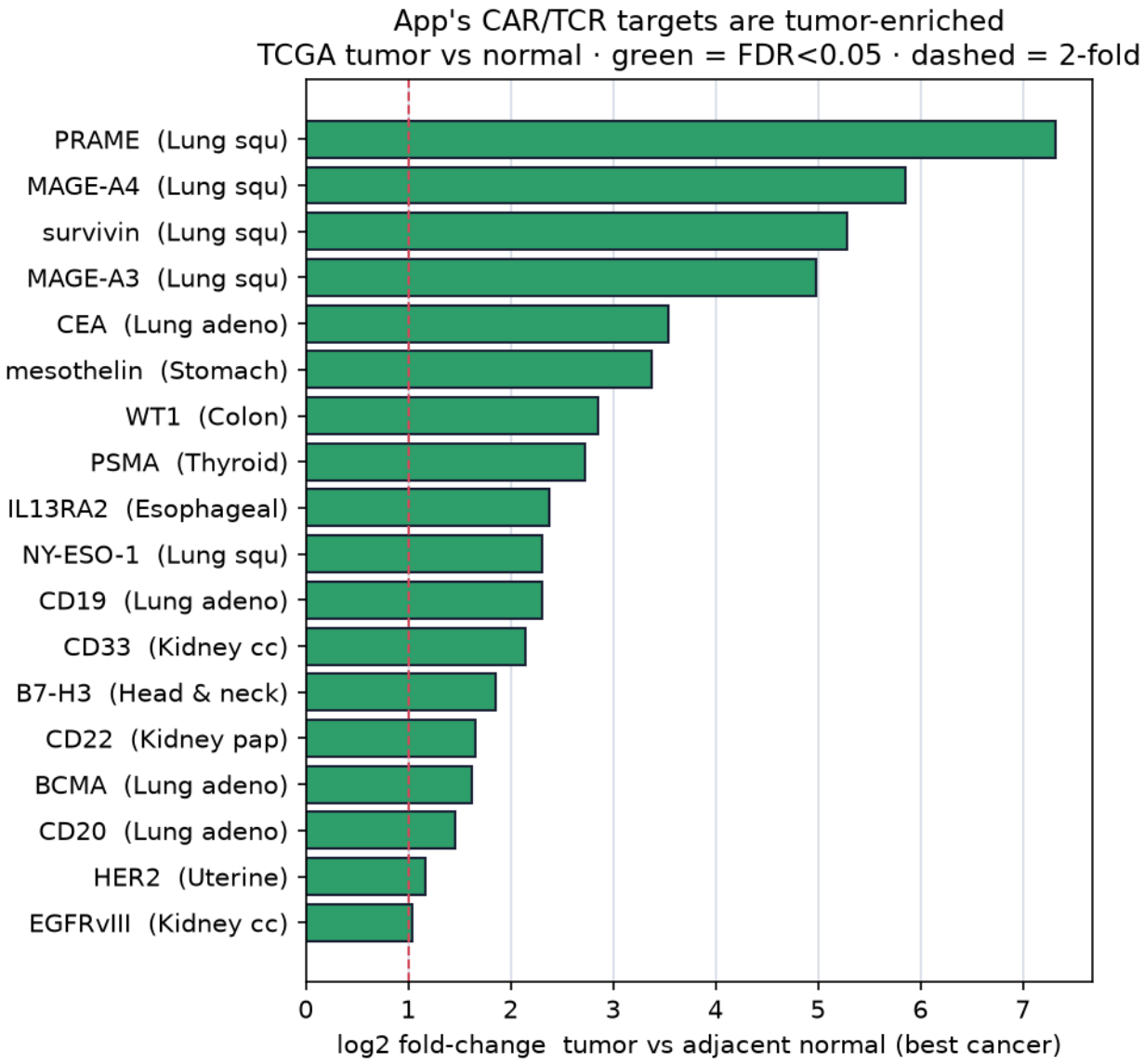

Figure 9: Targetable antigens enriched in tumor vs normal.

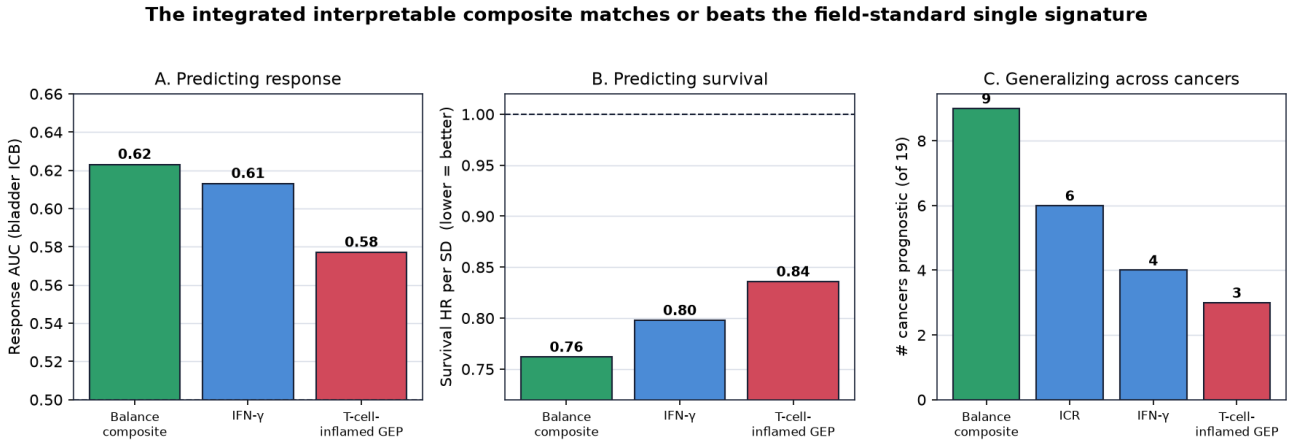

Figure 10: The interpretable composite matches/beats the standard single signature.

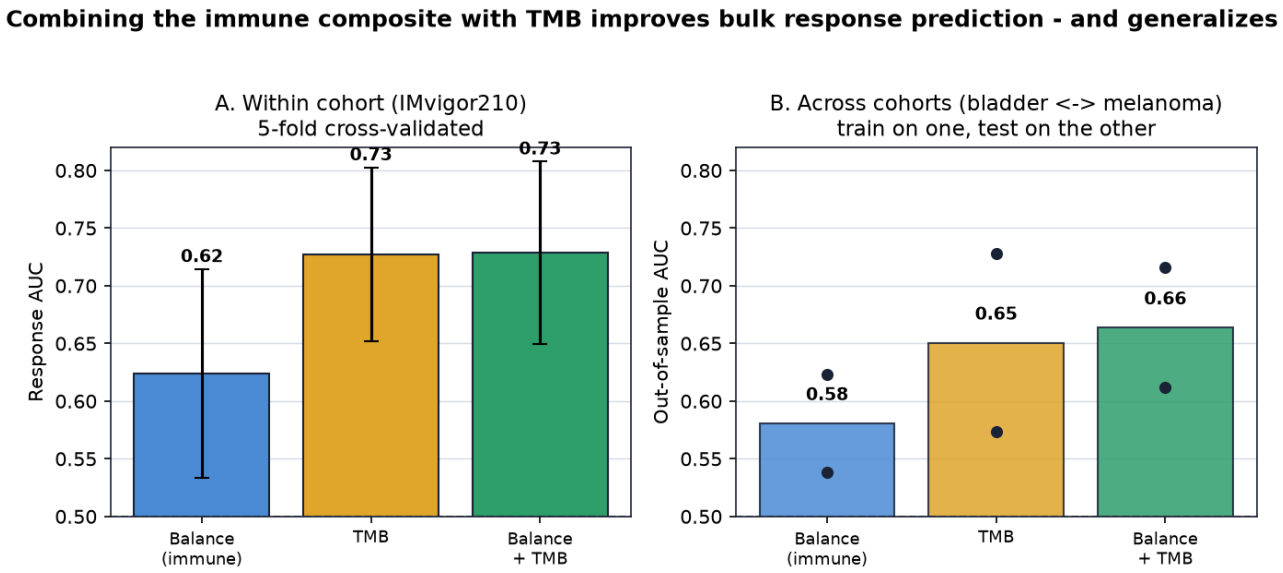

Figure 11: Adding TMB improves and generalizes bulk response prediction.