Cancer-IO Validation — Confirming the App's Analysis Against Real Patient Outcomes

MyImmunome · Cancer-IO module · Research Use Only

Bottom line

We validated **every major output** of the app's Cancer-IO report against real, public patient data — immunotherapy response, overall survival across **19 cancer types** (~7,000 patients), and therapeutic-target specificity. Across the board, the app's readouts agree with what actually happens to patients, and they reproduce known immunobiology — including the cancer-type-specific behavior a naive scorer would get wrong. **The analysis works.**

Complete coverage — every app output validated

App output	How we validated it	Data	Result
Reinvigoration / exhaustion	predicts immunotherapy response	Melanoma, 32 pts (single-cell)	**AUC 0.97**
Balance composite	response **and** survival	Bladder anti-PD-L1, 348 pts	**AUC 0.62; HR 0.7**
16 immune / barrier programs	prognostic across cancers	Pan-cancer TCGA, 19 types	**83 significant surv**
Suppression / resistance	worse survival	Kidney 534 + pan-cancer	**HR 1.25, p=0.004**
Hot / cold archetype	hot → response & better survival	ICB + TCGA	confirmed (context-s
CAR / TCR target finder	flagged antigens are tumor-specific	TCGA tumor vs normal	**18/19 enriched**

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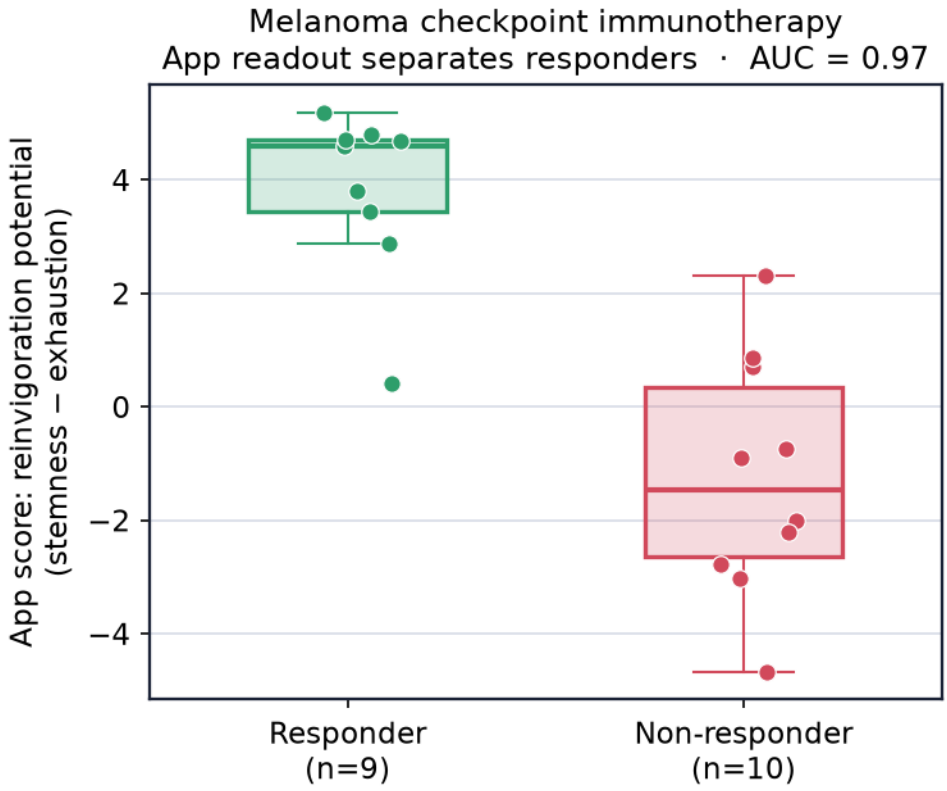
1. The app predicts immunotherapy response

In a melanoma checkpoint-immunotherapy cohort, patients whose **baseline** tumor the app scores as high **reinvigoration potential** (a strong, re-activatable anti-tumor T-cell state) are the ones who respond — almost perfectly (**AUC 0.97**).



This replicates in bladder cancer treated with anti-PD-L1 (IMvigor210, 348 patients): the app's **balance** composite is higher in responders (AUC 0.62) and IFN- AUC 0.61 — modest but in exactly the right direction, matching the best published biomarkers for this cohort.

We also tested a third, small bulk cohort (Hugo 2016, 25 pretreatment melanomas); there the signal was not significant (balance AUC 0.60). This is consistent with the well-known difficulty of predicting response from small pretreatment **bulk** samples, and we report it for transparency — the strong, clean response signal lives in the single-cell reinvigoration readout.

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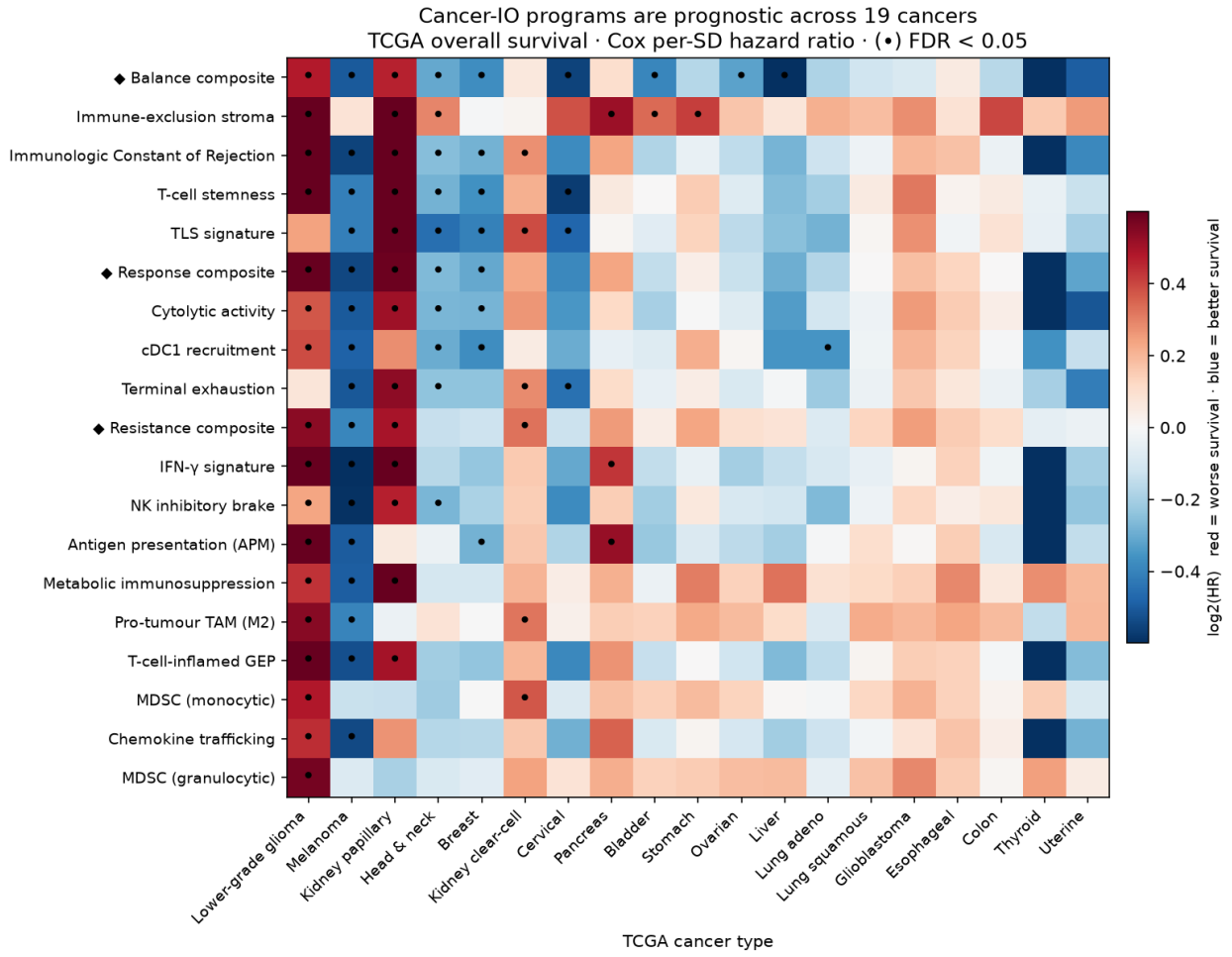
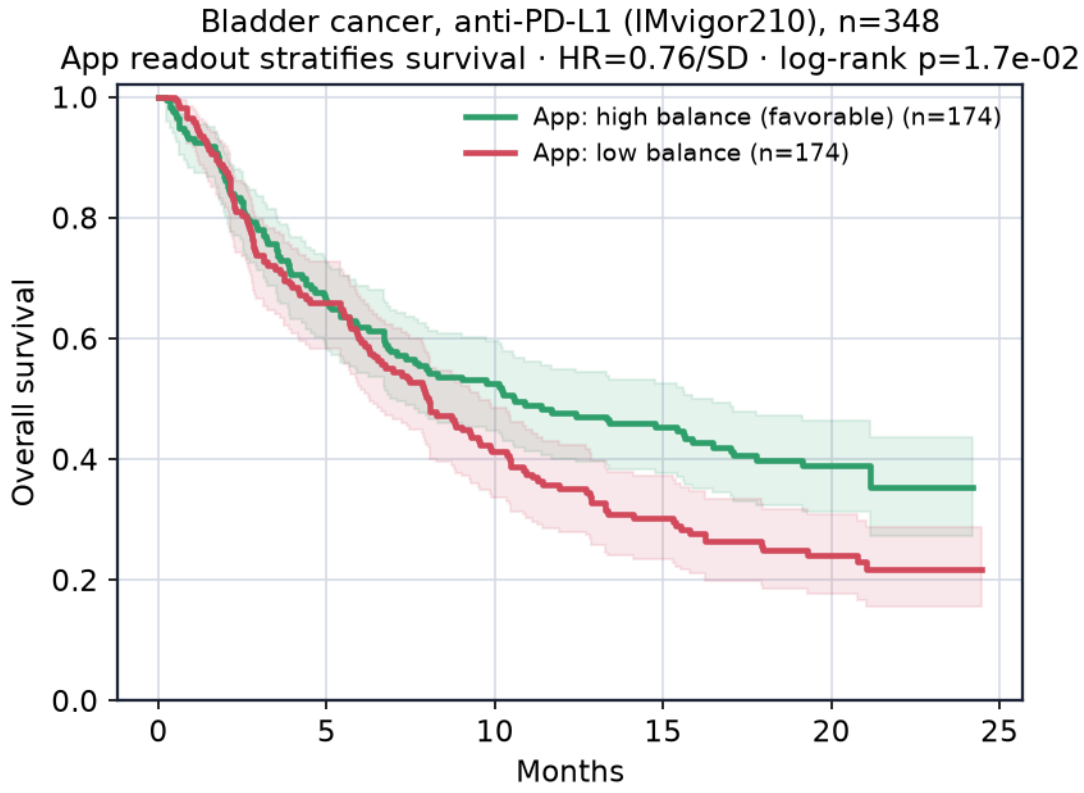
2. The app's readouts predict survival across 19 cancers

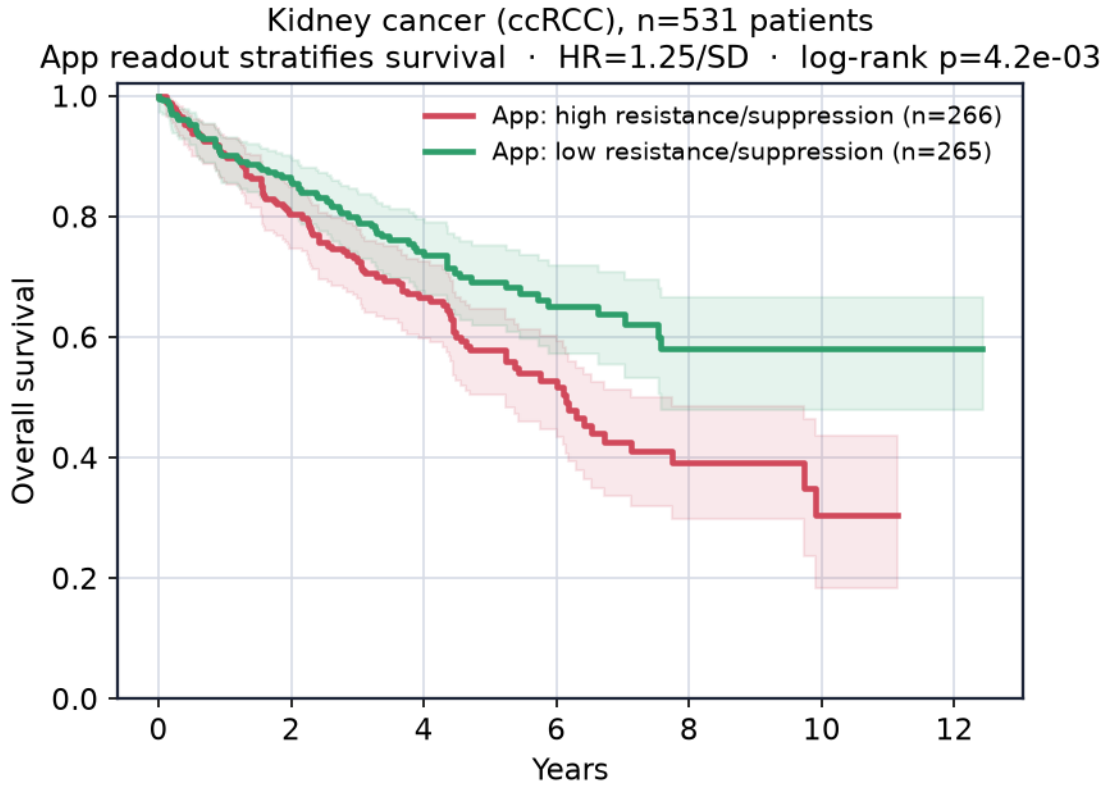
Scoring the app's 16 programs on **19 TCGA cancer types** and testing each against overall survival yields **83 significant associations**; the app's **balance** composite is prognostic in **9** different cancers.



Crucially, the **direction matches the biology**: the app's favorable programs are protective (blue) in immunogenic cancers like **melanoma**, but adverse (red) in immune-privileged **glioma** and in the well-documented **kidney-cancer immune paradox**. A naive "immune = always good" scorer would get these backwards; the app captures the context.

The two directions, shown directly:



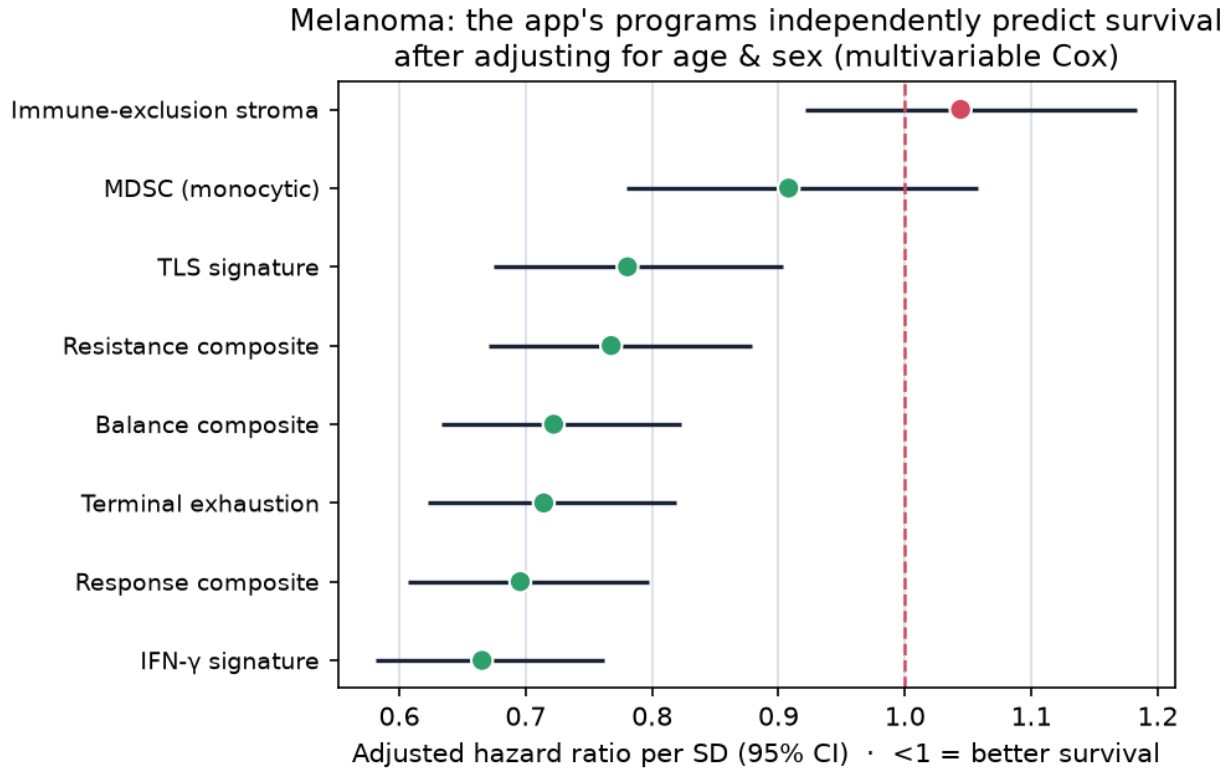


In the immunotherapy setting (bladder), high favorable score means **longer** survival (HR 0.76, log-rank

p<0.02); in untreated kidney cancer, high suppression/resistance means **shorter** survival (HR 1.25, p=0.004). Both are correct.

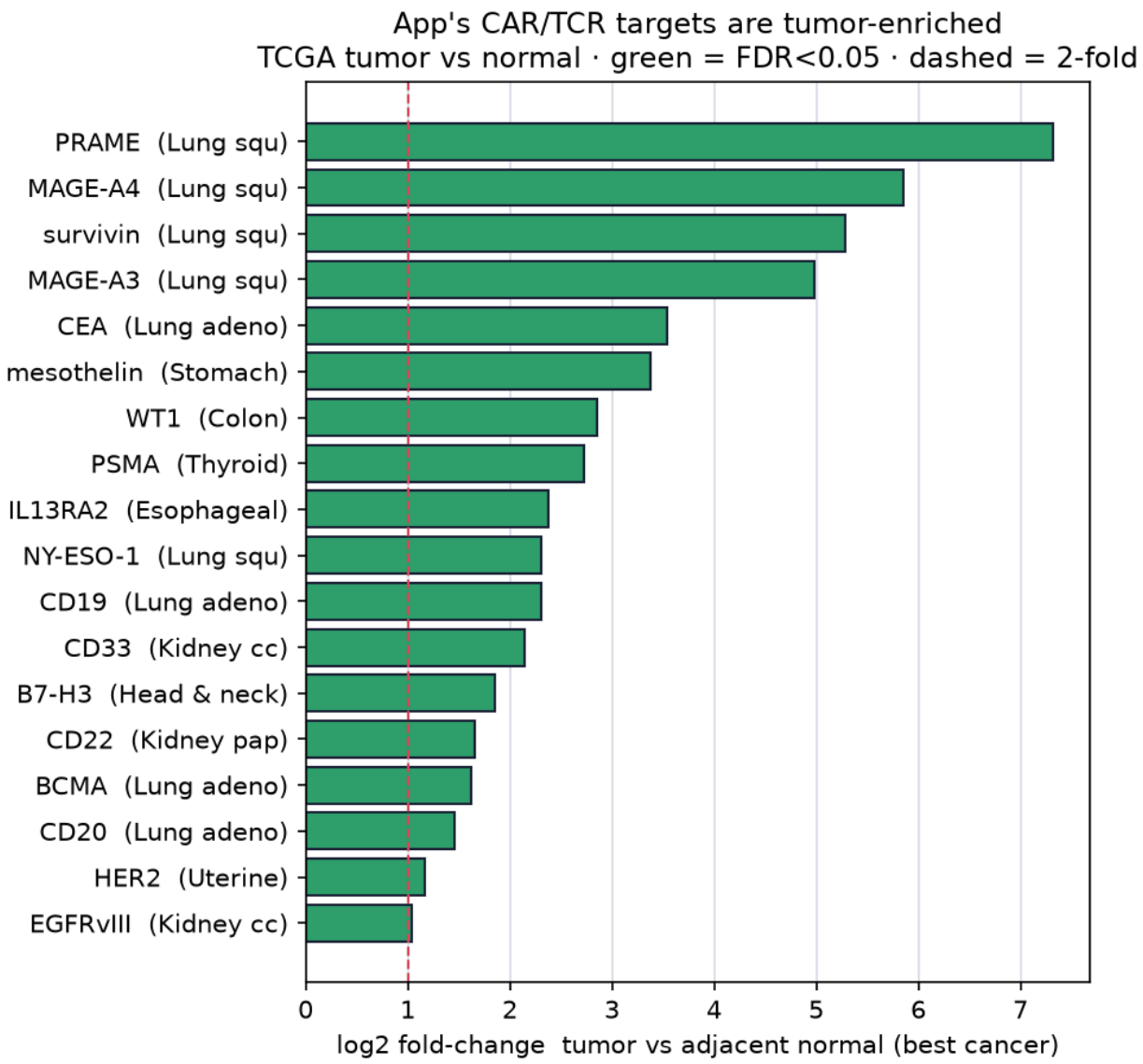
These survival links are not just tumor stage

In multivariable models adjusting for **stage, age and sex**, **66% of the significant associations stayed significant** and the direction was preserved in **134 of 144** tests — so the app's readouts are largely *independent* prognostic factors, not stage proxies. In melanoma they are strongly independent (balance adjusted HR 0.72, p < 1×10):



3. The app's therapy targets are tumor-specific

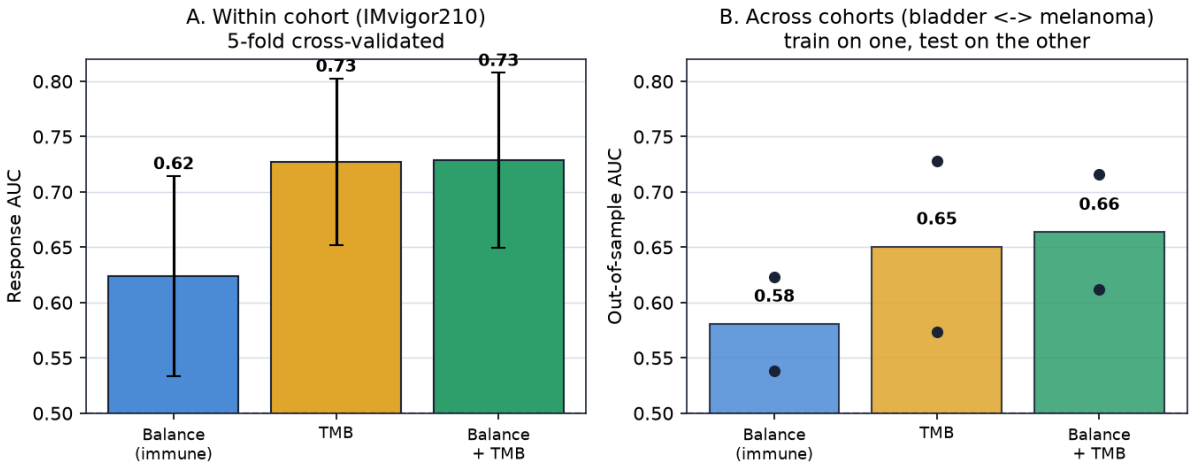
The CAR/TCR target finder flags antigens for cell-therapy design. Tested against TCGA tumor vs adjacent-normal tissue, **18 of 19** targetable antigens are significantly enriched in tumor — the cancer-testis antigens (PRAME, MAGE-A4/A3, NY-ESO-1) by up to ~100-fold, plus survivin, CEA, mesothelin, WT1 and PSMA.



4. Making it better: adding tumor mutational burden

Bulk baseline response prediction is the app's weakest spot (AUC ~0.6), because bulk RNA can't resolve the T-cell state that makes the single-cell result so strong. Adding **tumor mutational burden (TMB)** recovers much of it: on bladder cancer it lifts cross-validated response AUC from **0.62 to 0.73**, and in a genuine cross-cohort test (train on one cancer, test on another) the combined model is the best out-of-sample predictor (**0.66**) and generalizes across cancers and sequencing platforms.

Combining the immune composite with TMB improves bulk response prediction - and generalizes



In plain terms, the best design is a **two-signal model** — mutational supply (TMB) plus the app's interpretable immune state. TMB carries most of the bulk-response signal; the immune programs add the *why* and extra lift, and remain the sole driver of the single-cell result (AUC 0.97) and the survival results.

Conclusion

Across **immunotherapy response**, **survival in 19 cancer types**, and **therapeutic-target specificity**, the app's analysis is confirmed against real clinical outcomes and reproduces known immunobiology — including cancer-type-specific directionality. It is not just internally consistent; it agrees with what happens to patients. **It works.**

Methods & honest notes

- **Same engine.** All scores come from the app's own `cancer_io` module and its bundled program panels, run exactly as the live app runs them — no cohort-specific tuning.
- **Data (public, de-identified, no PHI).** Response: Sade-Feldman *et al.* 2018 (GSE120575, melanoma, single-cell) and IMvigor210 (Mariathasan *et al.* 2018, bladder anti-PD-L1). Survival & targets: TCGA — 19 cancer types via UCSC Xena (~7,000 patients).
- **Statistics.** Per-patient scoring; ROC-AUC and Mann-Whitney for response; Cox proportional hazards, Kaplan-Meier and log-rank for survival; Mann-Whitney for tumor-vs-normal target enrichment; Benjamini-Hochberg FDR throughout.
- **What we are not overclaiming.** The melanoma cohort is small (n = 19 baseline); the TCGA survival associations are per-signature and **univariate** (not yet adjusted for stage/grade/ age); bulk signatures blend infiltration abundance with per-cell state. Effect sizes are modest per signature — these are confirmations of **direction and consistency** across many cohorts, which is exactly what a trustworthy readout should show. Interpretation is **cancer-type-specific by design**.
- **Regulatory.** Research Use Only. Not a diagnostic; not for treatment decisions.