



Mining DepMap for Druggable Vulnerabilities in Esophageal Squamous Cell Carcinoma

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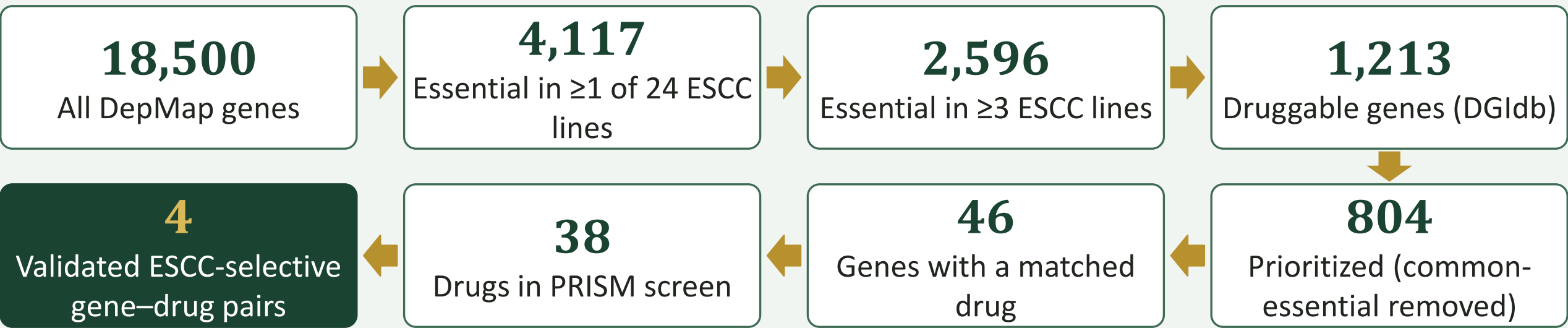
1 Introduction & Background

- ESCC is a major malignancy in the “esophageal cancer belt”, including northern Pakistan.
- Targeted options are limited; systemic therapy still relies largely on cytotoxic chemotherapy.
- DepMap uses genome-wide CRISPR knockout screens to find genes cancer cells need to survive.
- Gap: prior DepMap work analysed ESCC together with HNSCC, not as an independent cancer type.**

2 Objectives

- PRIMARY**
Identify ESCC-selective, druggable dependencies (DepMap); validate with PRISM.
- SECONDARY**
Identify existing drugs targeting these genes.
- HYPOTHESIS**
Matched drugs are more active in ESCC than other cancers.

3 Methodology: ESCC Vulnerability Prioritization Pipeline



Design: in-silico; DepMap 26Q1 CRISPR data (24 of 30 annotated ESCC lines; 25 with PRISM 20Q2 data; 23 overlap). Essential = Chronos ≤ -0.5 . **Tools & stats:** DGIdb, Open Targets; two-sample t-test ($p < 0.05$) and Pearson correlation.

4 Results: ESCC-Selective Drug Sensitivity

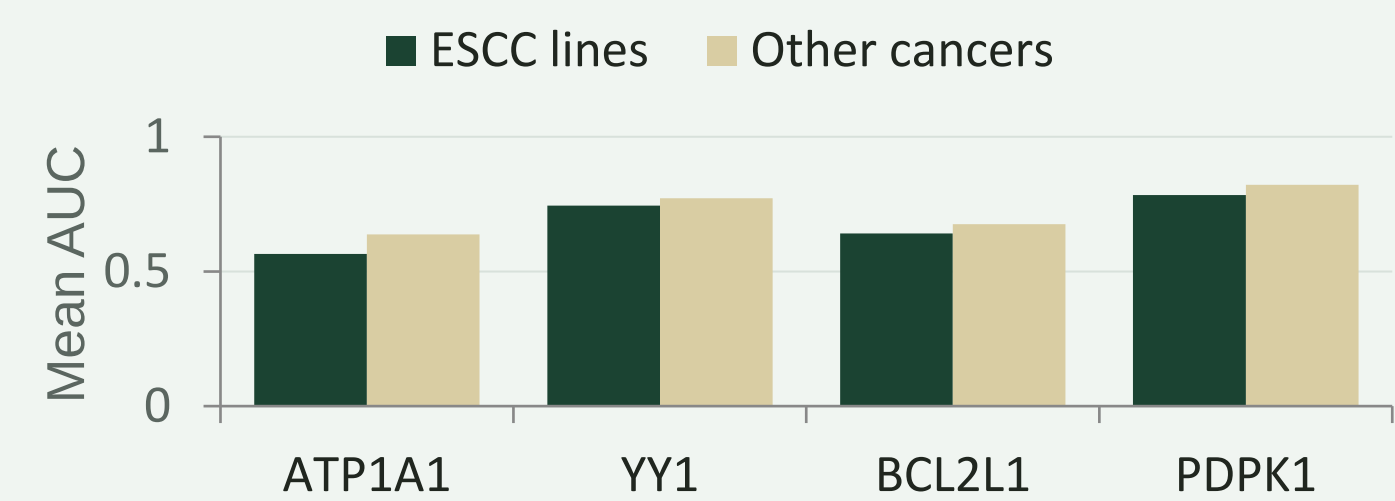


Figure 1. Mean PRISM drug-sensitivity AUC, ESCC vs. other cancer lines (lower = more sensitive). All four pairs $p < 0.05$.

Gene / Drug	ESCC	Other	p-value
ATP1A1 Digitoxin	0.565	0.637	2.4×10^{-5}
YY1 Belinostat	0.744	0.772	0.022
BCL2L1 Obatoclax	0.641	0.676	0.033
PDPK1 AR-12	0.784	0.821	0.035

Table 1. Mean PRISM AUC.

Strongest hit: ATP1A1 / digitoxin $p = 2.4 \times 10^{-5}$, an order of magnitude below the other three pairs.

5 Discussion

- Digitoxin/ATP1A1 is the top candidate; digoxin had no effect ($p = 0.97$), so the response is compound-specific.
- 3 more candidates significant in ESCC-only analysis.
- No predictive biomarker for digitoxin response ($r = 0.14$, $p = 0.58$).
- Limitations: small ESCC sample; incomplete core-fitness validation; no in-vivo or clinical validation.**

Conclusion

ATP1A1 / digitoxin is the strongest, statistically supported repurposing candidate.
Hypothesis-generating only: larger ESCC panels and experimental validation are needed.

References

1. Sannigrahi MK et al. Mol Oncol. 2024.

2. DepMap 26Q1, Broad Institute.

3. PRISM Repurposing 20Q2, Broad Institute.

4. DGIdb, dgidb.org.

5. Open Targets, opentargets.org.