Numenos AI, unleashing the power of clinical data

Pioneering the use of clinico-genomic foundation models for drug discovery

Pan-Cancer Immunotherapy Response Prediction using CURE AI

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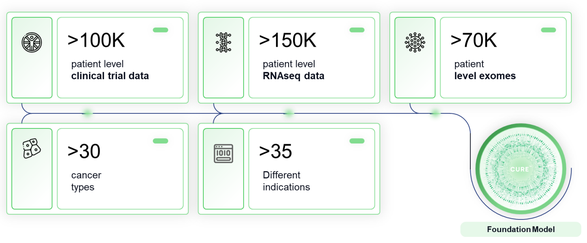
Abstract

Numenos developed a new type of deep learning platform that predicts patient response to cancer therapies. The large clinicogenomic model (LCGM), created by Numenos, is called Clinical trials Uncovering Real Efficacy Artificial Intelligence (CURE AI). CURE AI is trained on a large collection of clinicogenomic datasets to learn the complex relationships between the vast clinical and multiomic features in clinical trial data. Key innovations include: 1) A specialized deep learning architecture optimized for clinical trial data analysis; and 2) A novel training approach using large-scale clinical genomics datasets to enable accurate benefit prediction. However, we do not yet know of the potential limits of utilizing cross-cancer and pan-cancer predictions of immunotherapy response. In this study, we show initial validation of CURE AI for immunotherapy to predict cross-cancer benefit to immunotherapy over chemotherapy (non-small cell lung cancer to clear cell renal cancer, and clear cell renal cancer to non-small cell lung cancer). We demonstrate that a model finetuned on only JAVELIN Renal 101 trial data (avelumab plus axitinib versus sunitinib alone) leads to excellent stratification of non-small cell lung cancer patients for immunotherapy benefit, converting the Phase 2 POPLAR trial, which was negative for PFS, to a positive study if CURE AI eligibility criteria were utilized. Furthermore, we demonstrate that a model finetuned on only OAK and POPLAR lung cancer clinical trials (both testing atezolizumab versus docetaxel) improved statistical power and shortened time to trial approval for JAVELIN Renal 101. Finally, we demonstrate that CURE AI, finetuned on immunotherapy clinical trials, classifies a pan-cancer real-world dataset by predicted disease-site response, which stratifies into known, anticipated immunotherapy response categories. In summary, the CURE AI LCGM can utilize siloed clinical data to inform pan-cancer therapy response predictions. Use cases include providing evidence for indication expansion, developing custom models for improved combination therapy selection, and eligibility criteria customization for both early and late-line therapy settings. CURE AI has the potential to decrease clinical trial enrollment by over 50% through enhanced eligibility criteria selection while accelerating the time to find trial significance, which would dramatically accelerate progress in immunotherapy clinical trials.

One Solution, for any data type, or any indication



We bring data plus a foundation model to you!

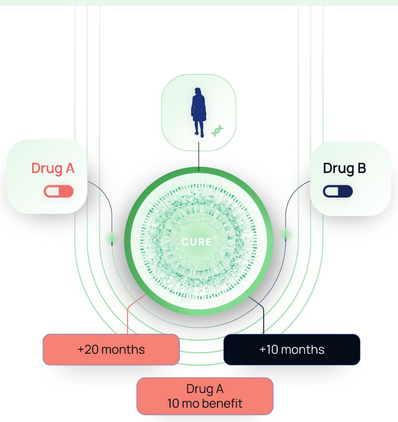
Input data can be a combination of client, public, or Numenos-acquired data

CURE AI predicts **untaken** drug effect **for each patient**

CURE AI calculates a counterfactual outcome for each patient to predict how they would have responded to the trial therapy that they did not receive.

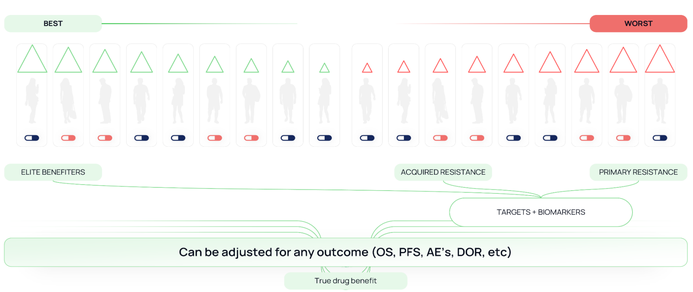
The difference in this predicted outcome allows the creation of a continuous response measurement, allowing an ordering of patients by predicted clinical benefit.

This allows us unparalleled insight into biomarker and target discovery, as we are able to minimize confounding variables.



CURE AI implements a Continuous Response Measurement

Comparing drug effects, not arms or responses!



The ordering of patients by their CURE AI Score is called the CURE Index.

OAK/POPLAR NSCLC to JAVELIN Renal 101 Prediction

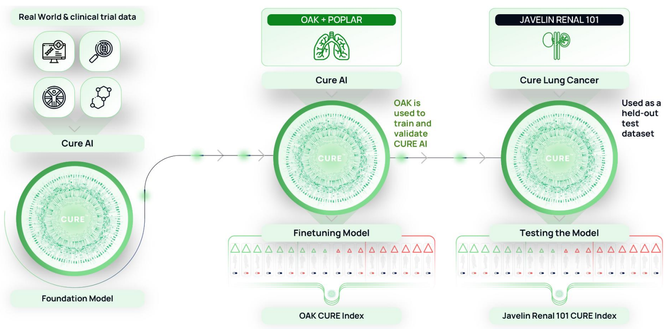


Figure 1. Outline of CURE AI Development, Finetuning, Validation and Testing in NSCLC and testing in ccRCC. The CURE AI foundation model was trained on vast clinical and multiomic datasets to learn and understand the interplay between clinical and multiomic features. CURE AI was applied to the aggregated OAK and POPLAR NSCLC clinical trials to finetune the model using CATE modeling and cross-validation to develop CURE Lung Cancer, a CURE AI model optimized on an immunotherapy NSCLC population. CURE Lung Cancer was then tested on the JAVELIN Renal 101 clinical trial in ccRCC to test if immunotherapy benefit prediction in lung cancer could predict therapeutic benefit in a different organ site (clear cell kidney cancer).

CURE Curve: Lung to Renal prediction

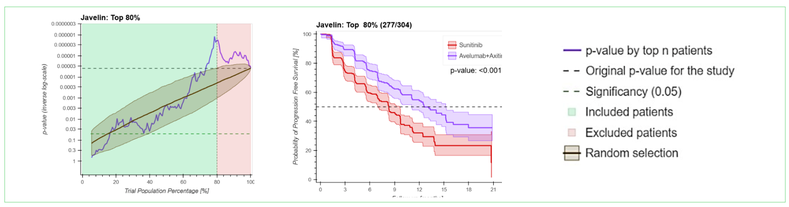


Figure 2. CURE Curve and Kaplan-Meier Estimates for the JAVELIN Renal 101 trial, using CURE Lung Cancer to organize ccRCC patients by predicted benefit to immunotherapy. The results indicate that information regarding immunotherapy response from NSCLC can predict immunotherapy benefit in ccRCC, a completely different cancer type, with minimal pretraining. This is seen most notably around the top 80% of patients where the p-value line has the highest peak (and lowest p-value).

Accelerated Approval Modeling: Lung to Renal

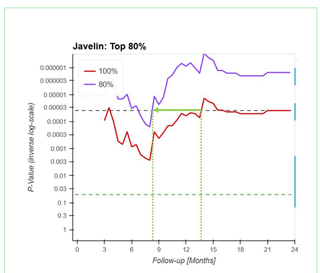


Figure 3. Accelerated Approval Modeling for CURE Lung Cancer on JAVELIN Renal 101. Using the best identified threshold (top 80% of patients with high predicted response to immunotherapy), we find that the trial could have reached is same final and stabilized p-value at 8.5 months instead of 13.5 months. If the trial would have been shortened by 5 months, with 20% fewer patients throughout the entire trial, significant cost savings could have been realized).

JAVELIN Renal 101 to OAK/POPLAR NSCLC Prediction

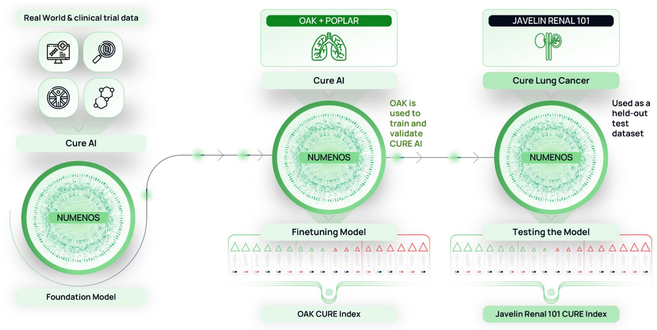


Figure 4. Outline of CURE AI training on ccRCC and testing on NSCLC. CURE AI was applied to the JAVELIN Renal 101 clinical trial to finetune the model using CATE modeling and cross-validation to develop a CURE AI model optimized on an immunotherapy ccRCC population (CURE Renal Cancer). CURE Renal Cancer was then tested on the POPLAR clinical trial.

CURE Curve: Renal to Lung

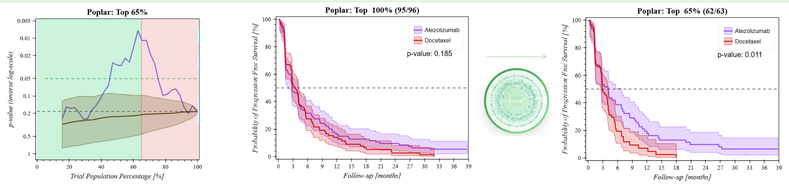


Figure 5. CURE Curve and KM Plots for the POPLAR NSCLC clinical trial, using CURE Renal Cancer to organize NSCLC patients. Using CURE Renal-stratification of patients on the POPLAR Trial, the top 65% of patients were selected for simulated enrollment. The resulting KM plots are shown, converting a negative clinical trial (p=0.185) to a positive study (p=0.011).

Accelerated Approval Modeling: Renal to Lung

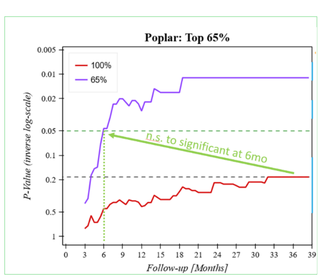


Figure 6. Accelerated Approval Modeling for CURE Renal Cancer on the POPLAR NSCLC trial. Using the best identified threshold (top 65% of patients with high predicted response to immunotherapy+TKI), we find that the trial could have reached is same final and stabilized p-value at 6 months instead of never reaching significance. This cross-cancer utilization of CURE AI is a dramatic use case of AI for cross-cancer data applicability and an example of data harmonization.

Cost savings from Accelerated Approval Modeling:
Dramatic reduction in trial size (20-70% reduction)
Faster time to approval (6-24 months)

CURE AI Pan-Cancer Predictions

Numenos

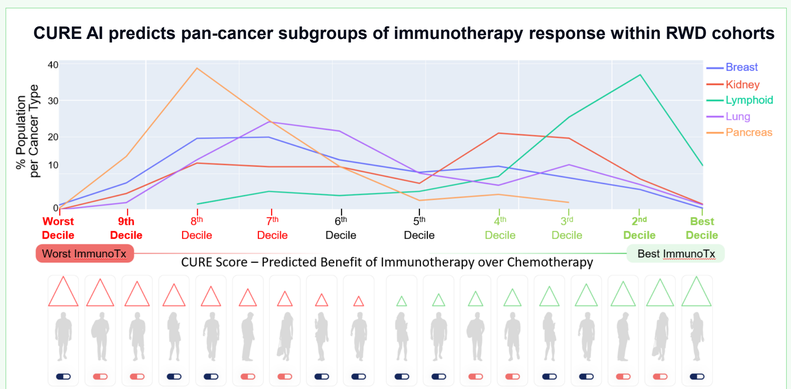


Figure 7. CURE Lung Cancer analysis of Real-World Data. CURE Lung Cancer (atezolizumab vs. docetaxel benefit) was used to analyze real-world data from RWD datasets in breast, kidney, lymphoid, lung, and pancreas cancer. Patients from each of the disease sites were combined into one group and assigned a CURE score based on their gene expression and available clinical features. Patients were sorted into deciles from best to worst, based on predicted benefit of immunotherapy over chemotherapy (based on the OAK and POPLAR atezolizumab versus docetaxel datasets). The percent of patients within each decile, per organ site, were plotted. CURE Lung Cancer sorted the RWD into what we would have predicted would be good or bad predicted responses favoring or disfavoring immunotherapy (pancreas disfavored; kidney and lymphoid favored; some breast and lung favored). The green deciles (top 40% of patients) most-favor immunotherapy.

CURE AI Biomarker Insights

- CURE AI - trained on lung or renal immunotherapy data - accurately predictions pan-cancer RWD immune responses.
- CURE AI can be utilized to deep-dive into these populations for R&D insights including biomarker discovery

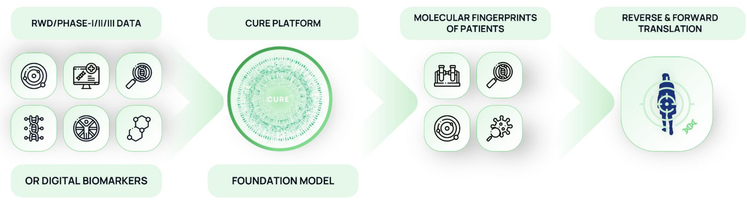
CURE AI Indication Expansion

- CURE AI can be utilized to deep-dive into these populations for R&D and indication expansion decisions.
- We can use your phase 2-3 clinical trial data to guide new drug therapy combinations, indication expansion decisions,

Clinical Trial Potential

- CURE AI is immediately available to guide clinical trial enrolment decisions
- We also facilitate interim trial analysis and adaptive trial design.
- Complete trial analysis can be completed in 6 weeks, facilitating rapid decision making for interim-trial design.
- We provide real world, patient-level evidence for new therapy combinations and adaptive trial decisions.
- CURE AI can be employed as a complex model as well as a simplified, distilled model for patient enrolment/recruitment.

Summary & Key Value Proposition



Forward translation value
- Cross indication response prediction
- Indication expansion & prioritization
- Endotype-driven patient enrichment

Reverse translation value
- Identify unmet needs
- Identify foundational targets
- Target population identified in advance for therapeutic differentiation

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