RADR™ : Establishment of a Drug-Tumor Interaction Database using Lantern Pharma's Response Algorithm for Drug Positioning and Rescue (RADR™)

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Abstract

The Response Algorithm for Drug positioning and Rescue (RADR™) technology is Lantern Pharma's proprietary Artificial Intelligence (AI)-based machine learning approach for biomarker panel identification and patient stratification. RADR™ is a combination of three automated modules working sequentially to generate drug- and tumor-specific gene signatures predictive of response. RADR™ integrates biological knowledge, data-driven feature selection, and robust AI algorithms to facilitate hypothesis-free, drug- and cancer-specific biomarker development. RADR™ uses transcriptomic, drug sensitivity datasets and systems biology inputs and generates gene expression-based responder/ non-responder profiles for specific tumor indications with high accuracy. RADR™ uses a unique process flow and a combination of machine learning algorithms to extract drug-specific biomarkers from whole transcriptome level input (~18000 genes). Using RADR™ we have created a database of drug response prediction models for more than 120 drug-tumor type combinations in a preclinical setting that is expected to keep growing. These drug- and cancer-specific RADR™ models have further enabled the classification of clinical records into distinct response groups, as well as generated gene expression signatures as features predictive of therapy response. The value of the platform architecture is derived from its validation through the analysis of about 16 million oncology-specific clinical data points, more than 120 drug-cancer interactions, and over 900 patient records. The average response prediction accuracy lies above 80%. This database links the majority of FDA approved and selected investigational drugs with appropriate cancer indications and the associated RADR™-derived responder/ non-responder profiles in terms of gene expression signatures. This database could directly inform the drug-companion diagnostic co-developmental pathways for new drugs and cancer indications.

Challenges

Lantern Pharma is harnessing the power of artificial intelligence to sift through massive datasets and identify biomarkers related to complex cancers. Several challenges include:

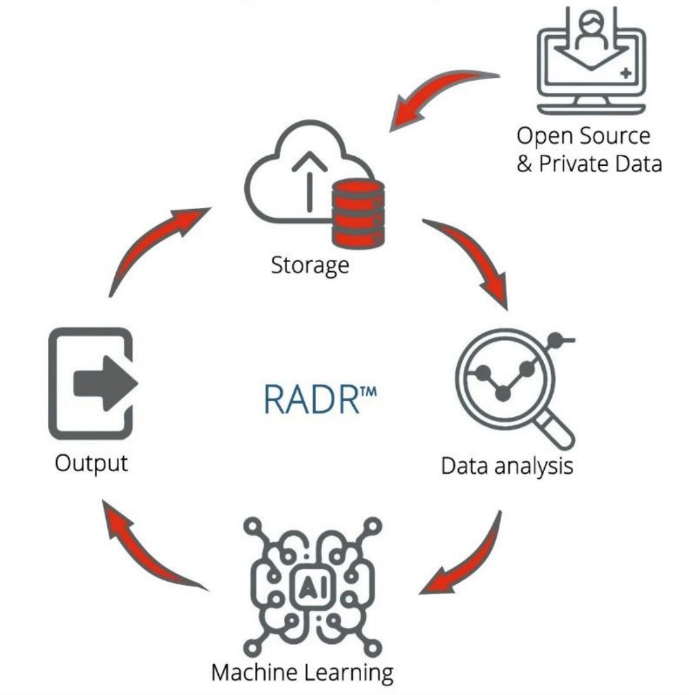
- Using big data and artificial intelligence to discover new anticancer therapeutics showing enhance clinical benefit in selected patient populations
- Using publicly available omics datasets, drug response datasets, and independent datasets to construct and train optimized machine learning-based models
- Processing large data sets with extreme care to identify and validate clinically-relevant predictive biomarkers

Lantern Pharma's RADR™ technology has been developed by considering all these aspects. The platform has demonstrated remarkable drug response prediction accuracy in clinical validation and continues to be optimized for improved performance.

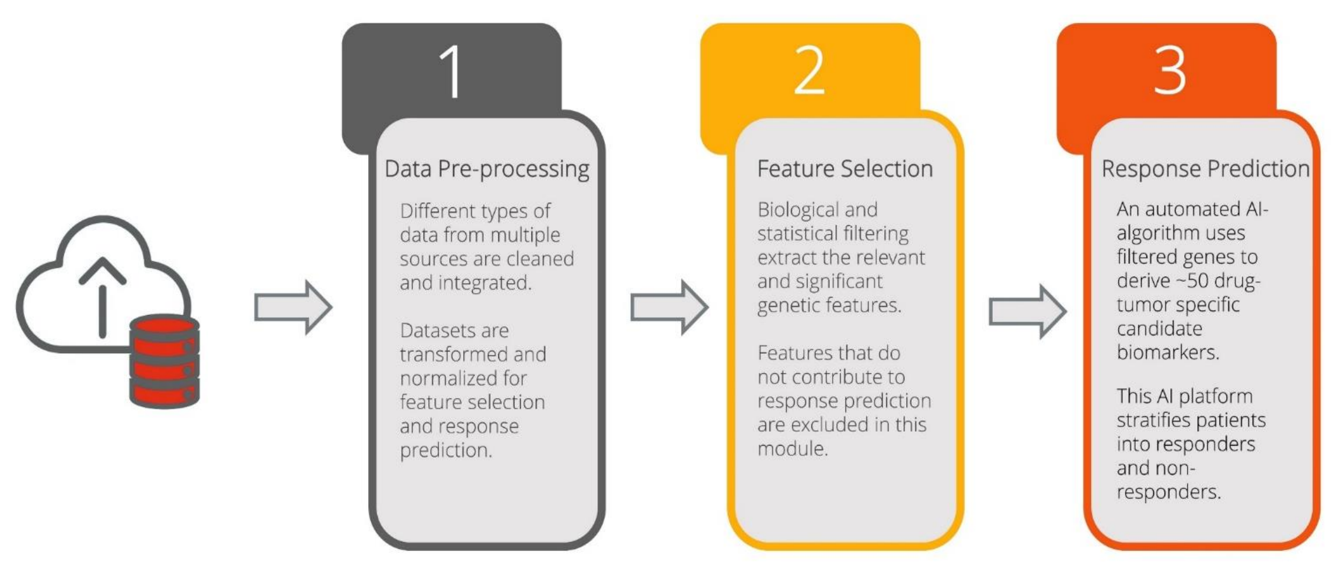
Objectives

- Develop genetic feature selection methodologies that can be game changing in the development of Companion Diagnostics (CDx) for oncology patient management
- Derive a robust, validated and biologically meaningful genomic signature to predict the potential for a patient to respond to a specific cancer drug
- Stratify patients prospectively using RADR™-derived genomic and biomarker analysis for greater success, and lower cost in clinical trials

RADR™ Process Architecture



RADR™ Modules



1 Data Pre-processing
Different types of data from multiple sources are cleaned and integrated.

Datasets are transformed and normalized for feature selection and response prediction.

2 Feature Selection
Biological and statistical filtering extract the relevant and significant genetic features.

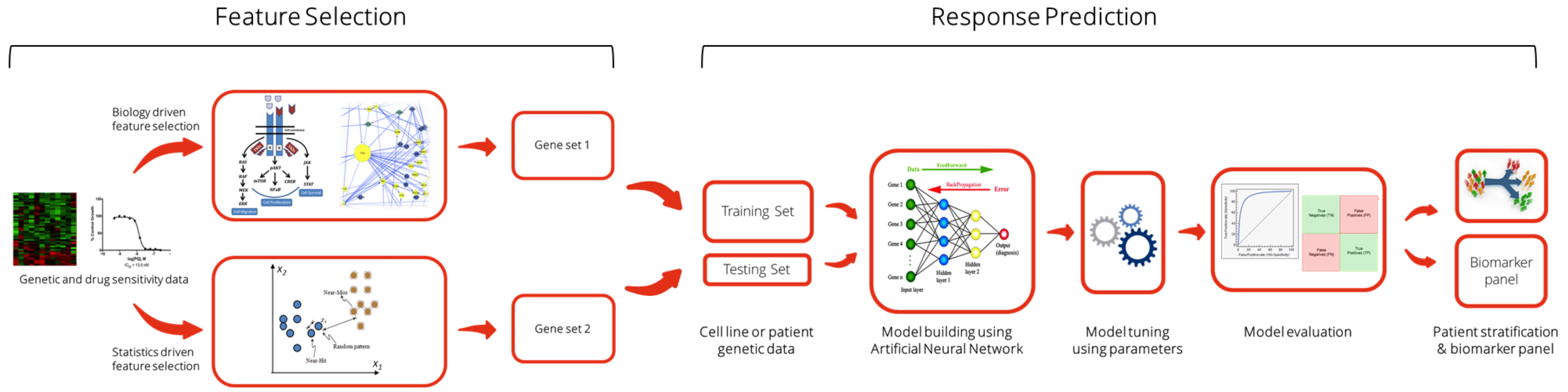
Features that do not contribute to response prediction are excluded in this module.

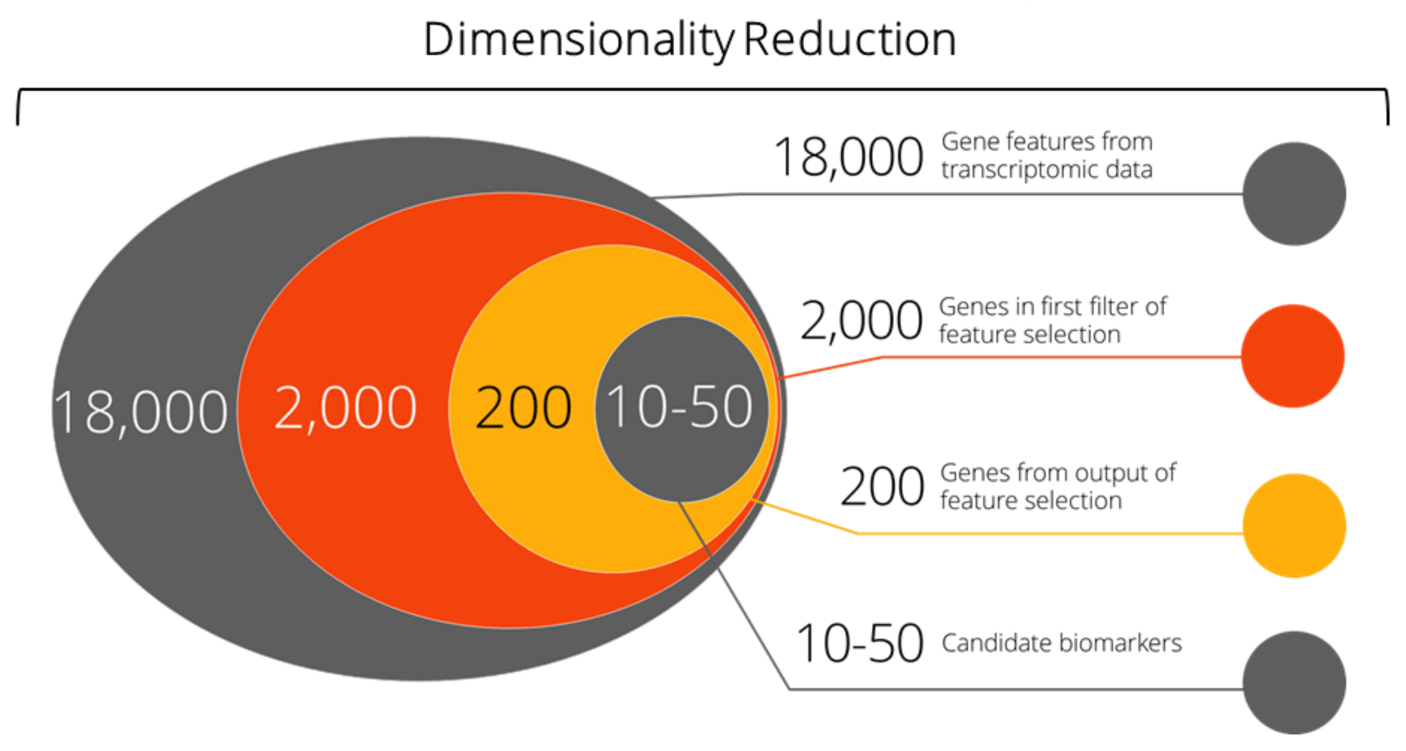
3 Response Prediction
An automated AI-algorithm uses filtered genes to derive ~50 drug-tumor specific candidate biomarkers.

This AI platform stratifies patients into responders and non-responders.

Technology

RADR™'s AI-based machine learning approach for hypothesis-free biomarker identification and patient stratification is a combination of three sequential automated modules. These modules displayed in Figures 1 and 2, include data pre-processing, feature selection, and response prediction.

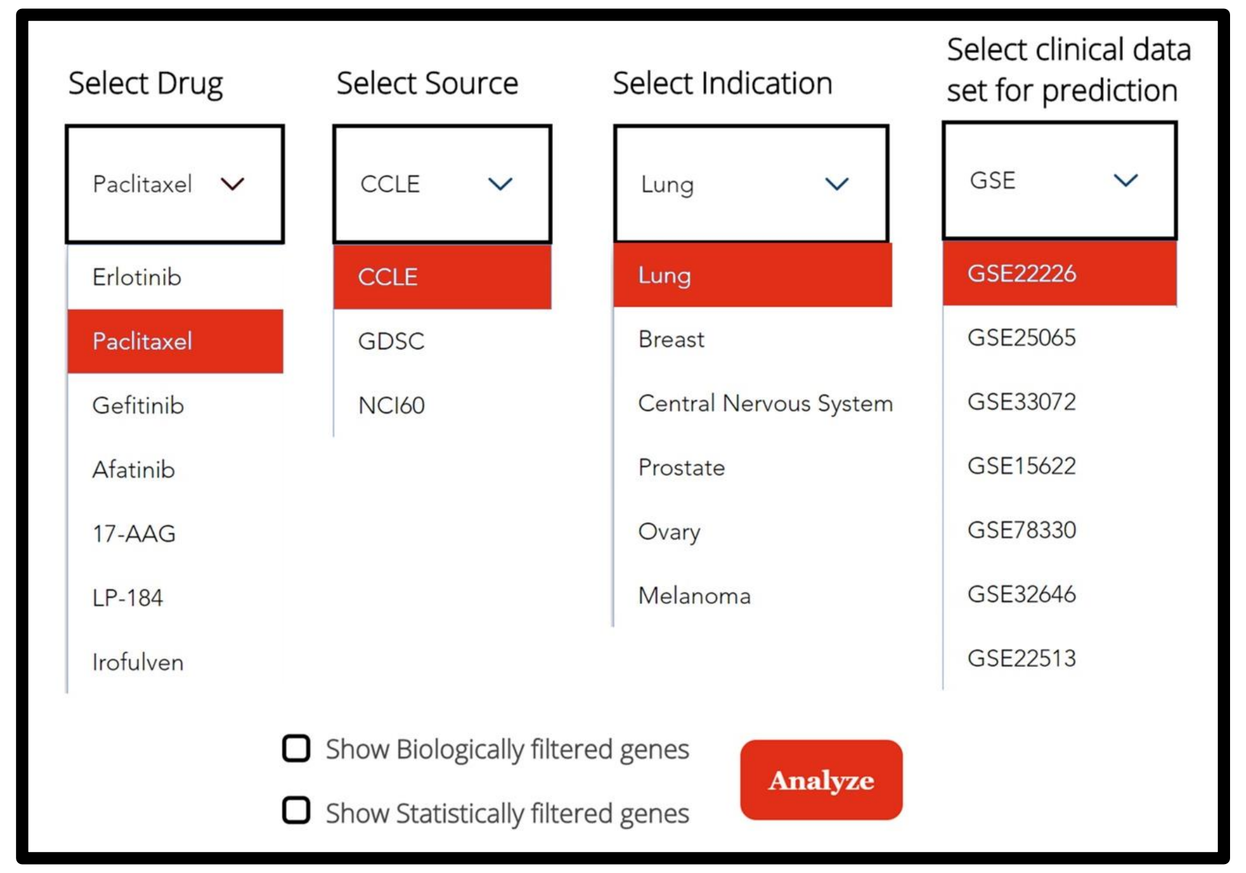


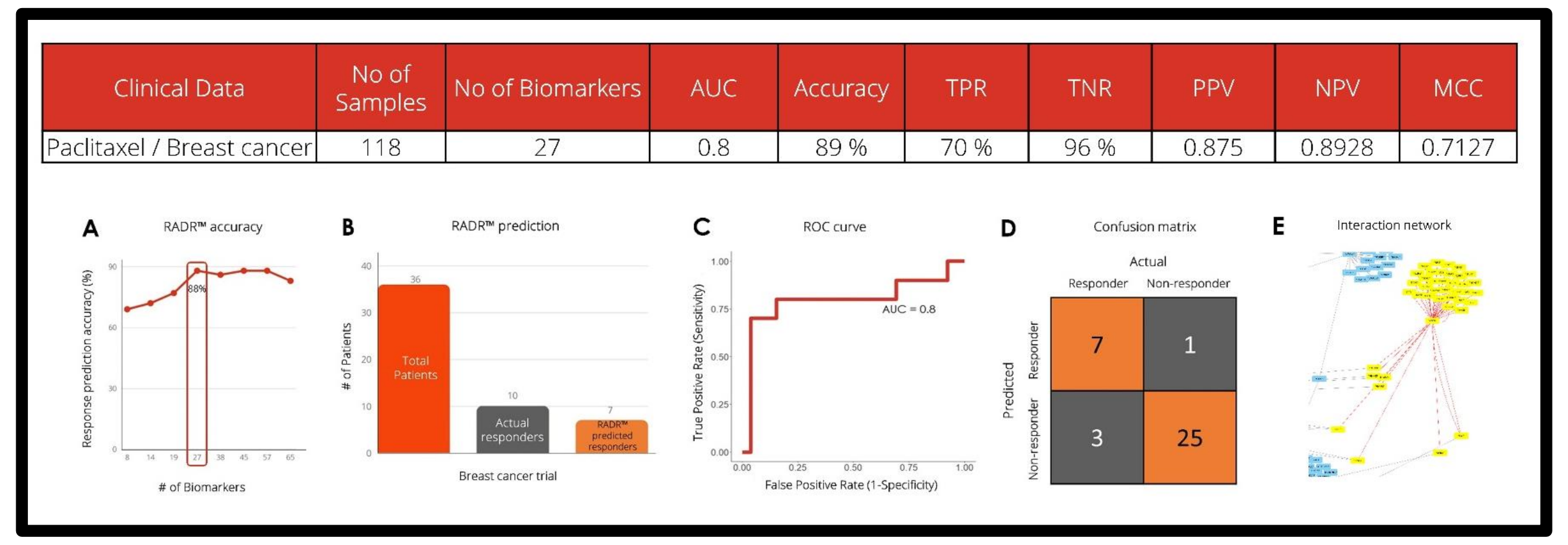


RADR™'s proprietary process performs preliminary statistical analysis on ~18000 features typically from whole transcriptomic datasets reducing the set to ~2000 features. This is followed by gene filtering via biological and statistical methodologies yielding ~200 significant genes. Feature selection ensures that genes that do not contribute to response prediction are excluded from the output dataset. The prediction component subsequently applies an AI-driven reduction algorithm to the previously filtered genes (~ 200), generating a targeted set of typically less than 50 candidate biomarkers predictive of response to a particular drug.

Using proprietary gene feature selection methodologies, the RADR™ platform derives drug and tumor type-specific candidate biomarkers associated with response to a particular cancer therapy.

Planned interface of the RADR™ database





Clinical Data	No of Samples	No of Biomarkers	AUC	Accuracy	TPR	TNR	PPV	NPV	MCC
Paclitaxel / Breast cancer	118	27	0.8	89 %	70 %	96 %	0.875	0.8928	0.7127

Planned web portal being designed to compile and display the working and outcomes of RADR™. The interface is user-friendly and allows selection of the platform application to a drug, cancer type or dataset of interest. The above is an example of prediction of Paclitaxel clinical response in breast cancer. Such a web portal will facilitate further understanding of drug-specific response biomarkers and provide insight into gene signature dependent drug repositioning or combination opportunities.

Foundations of RADR™ platform building

RADR™ is built on aggregating data, and the platform becomes more robust as datasets are added. It covers multiple cancer types and drug classes while delivering consistent prediction accuracy outputs. RADR™ models built and trained on preclinical datasets are fine-tuned and cross-validated on clinical datasets for specific drug-tumor interactions.

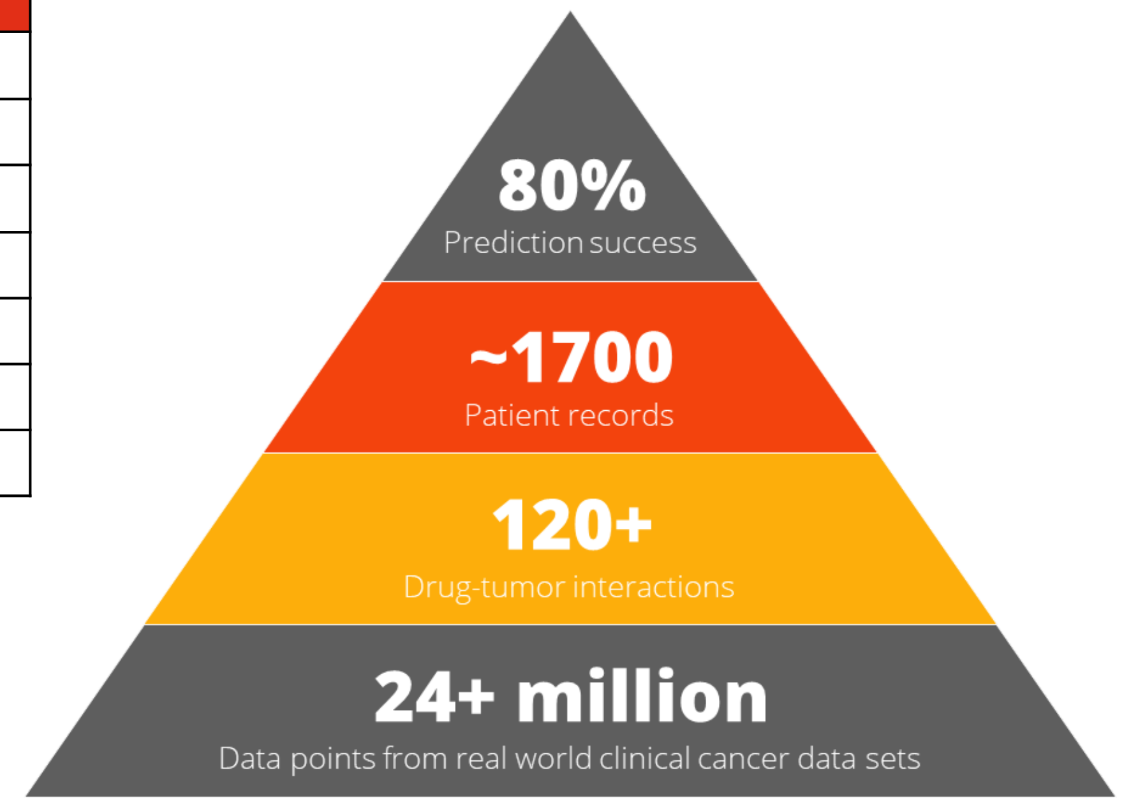
RADR™ preclinical analyses by drug class and cancer type

Drug class	Approval status	Drug name	Cancer Indication	# of records	Overall prediction accuracy (%)
Chemotherapy	Approved	Topotecan	Lung	82	88
Targeted therapy	Non approved	Panobinostat	Hematological	70	100

Cancer type	# of drug-tumor interactions
Breast	16
Central Nervous System	17
Hematopoietic & lymphoid tissue	30
Intestine	6
Kidney	1
Lung	47
Ovary	5

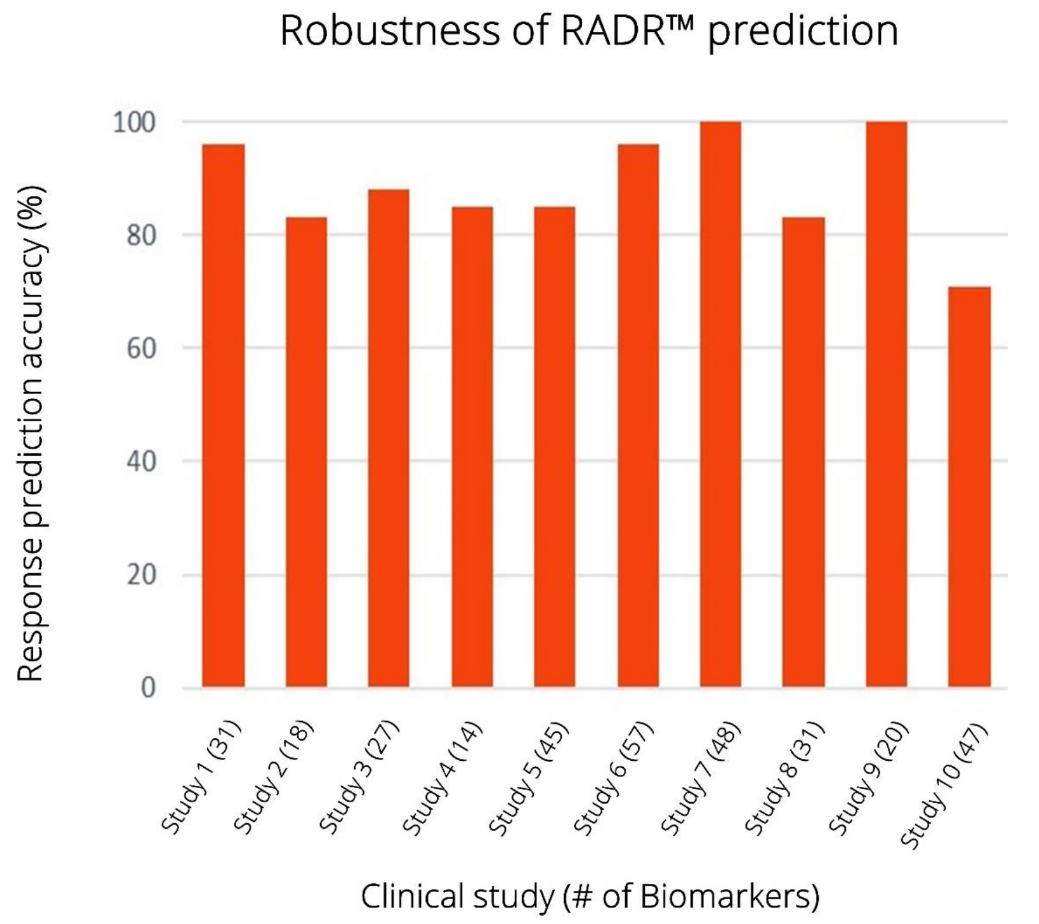
Drug class	# of drug-tumor interactions
Chemotherapy	27
Targeted therapy	98

RADR™ capability and success



Key findings and future perspectives

Candidate biomarker identification and performance of RADR™ during clinical validation



Study #	Drug(s)	Cancer indication	Ref
1	Paclitaxel	Breast	1
2	Paclitaxel	Breast	2
3	Paclitaxel	Breast	3
4	Paclitaxel	Ovarian	4
5	Paclitaxel + FEC	Breast	5
6	Paclitaxel + FAC	Breast	6
7	Erlotinib	Lung	7
8	Sorafenib	Lung	7
9	Keytruda	Melanoma	8
10	Tamoxifen	Breast	9

- RADR™ has achieved a prediction accuracy rate greater than 80% in 10 independent clinical studies.
- RADR™ aims to incorporate multi-omics datasets covering preclinical and clinical mutational, proteomic and epigenetic profiles.
- Lantern intends to rescue, reposition or repurpose the extensive library of failed and abandoned oncology drugs by leveraging the power of its RADR™ platform.

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