Clinical Validation of Lantern Pharma's Response Algorithm for Drug Positioning and Rescue (RADR™)

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Abstract

Lantern Pharma has developed a technology platform termed RADR™ that can be used to predict true responders before conducting a clinical trial in order to achieve higher success rates. RADR™ is an Artificial Intelligence (AI)-based machine learning approach for complex biomarker 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. We present retrospective analyses performed as part of RADR™ validation using at least 9 independent datasets of patients from selected cancer types treated with approved drugs including chemotherapy, targeted therapy and immune-oncology agents. Pre-treatment patient gene expression profiles along with corresponding treatment outcomes were used as algorithm inputs. Model training was typically performed using an initial set of genes derived from cancer cell line data when available, and further applied to a subset of patient data for model tuning and final gene signature development. Model testing and performance computation were carried out on patient records held out as blinded datasets. The response prediction accuracy, true positive rate (TPR), true negative rate (TNR) false discovery rate, positive predictive value and Matthew's Correlation Coefficient were among the model performance metrics calculated. On average, RADR™ achieved a response prediction accuracy of 80% during clinical validation. For instance, in an analysis of 92 breast cancer patients, RADR™ generated a signature of 18 genes whose expression level was predictive of Paclitaxel treatment response at an overall accuracy of 78% and 81% TPR/ 76% TNR. The above results imply that the application of the RADR™ program to this Paclitaxel trial in breast cancer patients could have potentially reduced the number of patients in the treatment arm from 92 unselected patients to 24 biomarker-selected patients to produce the same number of responders. Moreover, we cite published evidence correlating genes from this 18-gene signature with increased Paclitaxel sensitivity in breast cancer. The value of the platform architecture is derived from its validation through the analysis of about 6 million oncology-specific clinical data points, more than 120 drug-cancer interactions, and over 600 patient records. Thus, by implementing unique biological, statistical and machine learning workflows, Lantern Pharma's RADR™ technology is capable of deriving robust biomarker panels for pre-selecting true responders for recruitment into clinical trials which may improve the success rate of oncology drug approvals.

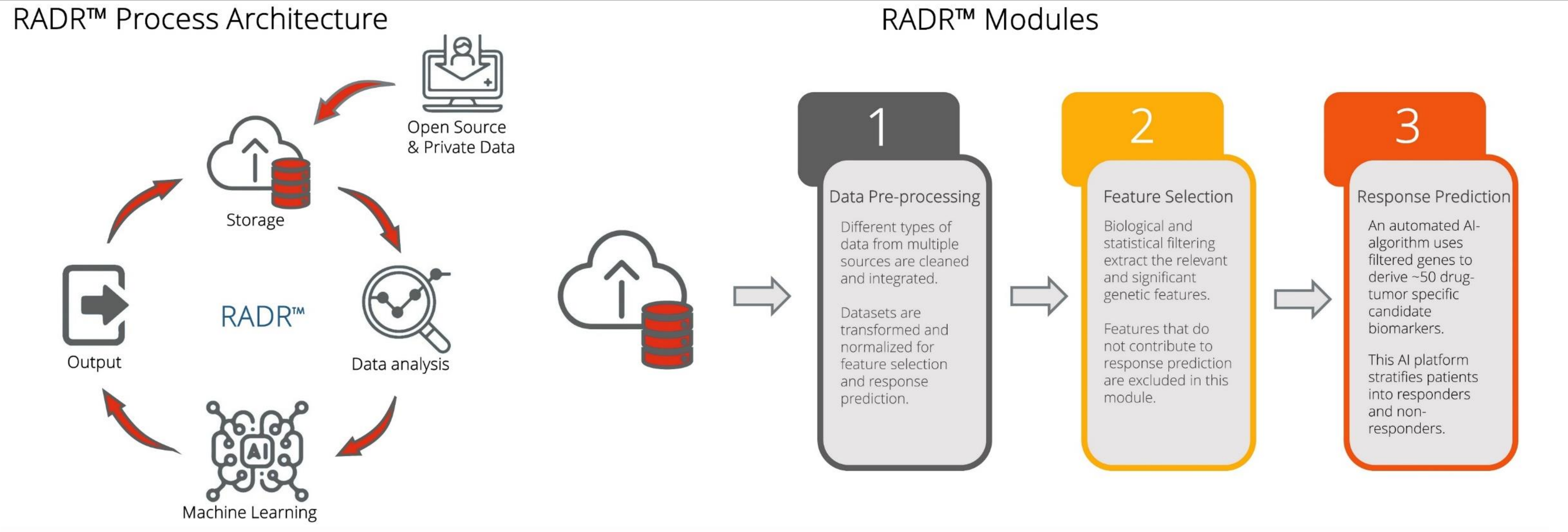
Challenges

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 enhanced 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.

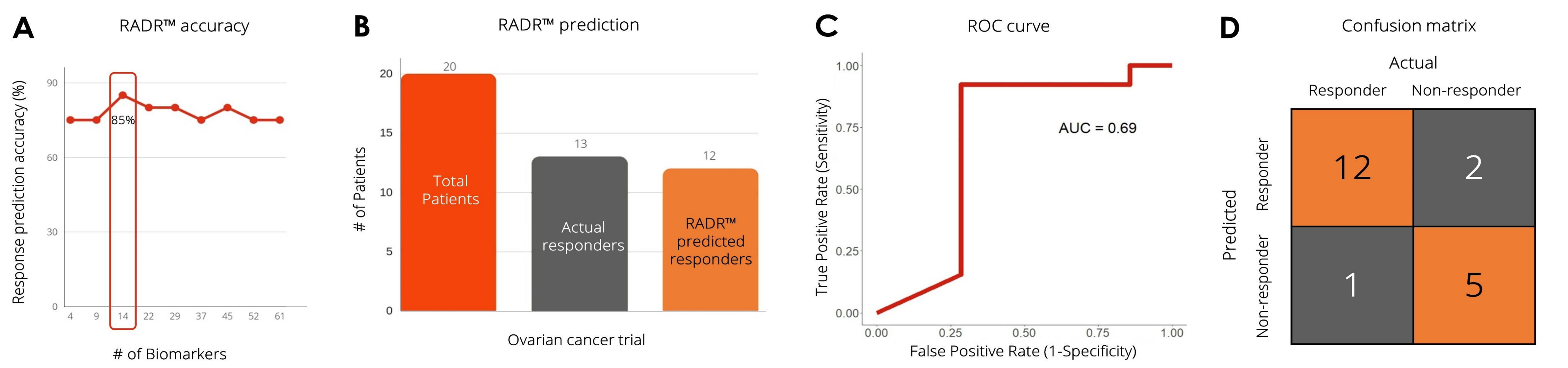
RADR™ Technology Overview



Objectives

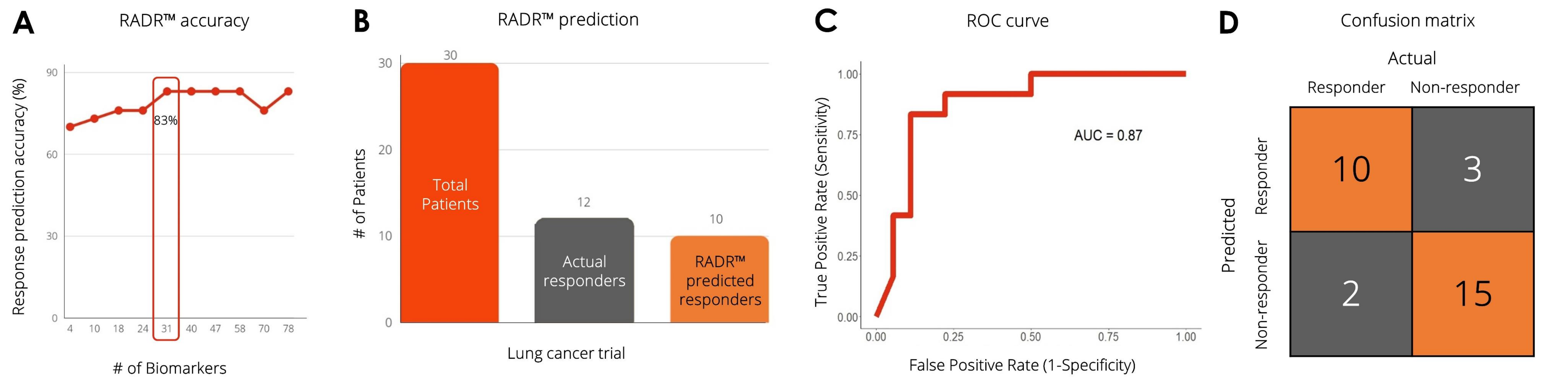
- Develop machine learning-based model building and fine-tuning workflows that can integrate preclinical and clinical drug response and transcriptomic datasets
- Evaluate multiple model performance metrics for each drug-tumor interaction
- Derive a validated genomic signature capable of predicting the potential for a patient to be classified as a responder or non-responder to a specific cancer drug

Clinical Case Study 1 - Paclitaxel / Ovarian Cancer


A
RADR™ accuracy
Response prediction accuracy (%)
85%
# of Biomarkers
B
RADR™ prediction
# of Patients
Total Patients
Actual responders
RADR™ predicted responders
20
13
12
Ovarian cancer trial
C
ROC curve
True Positive Rate (Sensitivity)
AUC = 0.69
False Positive Rate (1-Specificity)
D
Confusion matrix
Actual
Responder
Non-responder
Predicted
Responder
Non-responder
12
2
1
5

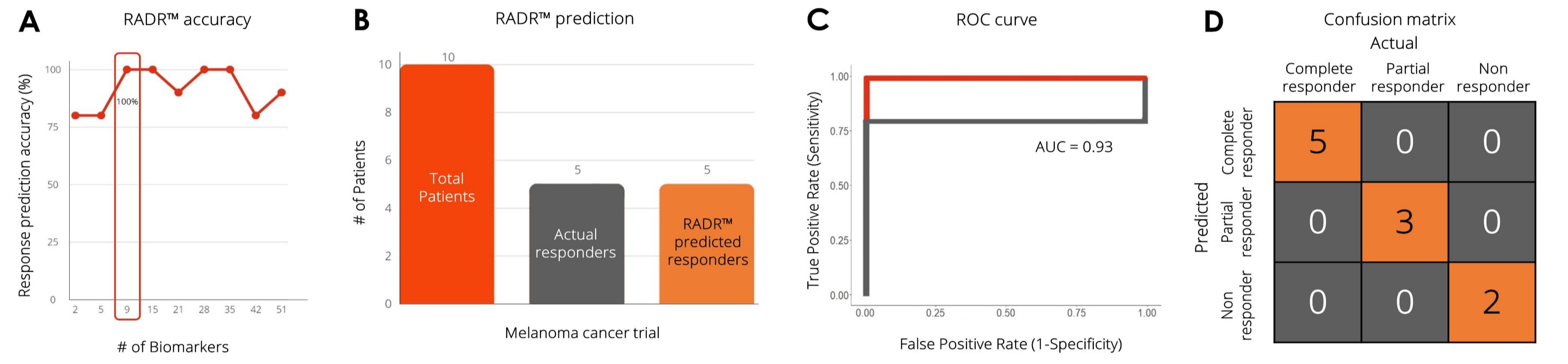
Retrospective analysis of 35 Paclitaxel treated ovarian cancer patients [1] was performed using RADR™. Figure 1A highlights the comparison of response prediction accuracy across a range of biomarker numbers in this clinical study. Starting from >16,000 genes, RADR™ identified a 14-gene signature in ovarian cancer patients as predictive of response to Paclitaxel treatment with an accuracy of 85%. As depicted in Figure 1B, out of 20 patients included in the blinded test set, RADR™ correctly predicted 12 out of 13 actual responders (92% true positive rate). Figures 1C and 1D show model performance metrics such as area under curve (AUC) and confusion matrix representation, respectively. Model training was performed using an initial set of 212 genes derived from Paclitaxel-ovarian cancer cell line data, further applied to data from 25 cell lines and 15 patients for model tuning and final gene signature development. Model testing was conducted on 20 patient records isolated as the blinded hold-out set.

Clinical Case Study 2 - Sorafenib / Lung Cancer


A
RADR™ accuracy
Response prediction accuracy (%)
83%
# of Biomarkers
B
RADR™ prediction
# of Patients
Total Patients
Actual responders
RADR™ predicted responders
30
12
10
Lung cancer trial
C
ROC curve
True Positive Rate (Sensitivity)
AUC = 0.87
False Positive Rate (1-Specificity)
D
Confusion matrix
Actual
Responder
Non-responder
Predicted
Responder
Non-responder
10
3
2
15

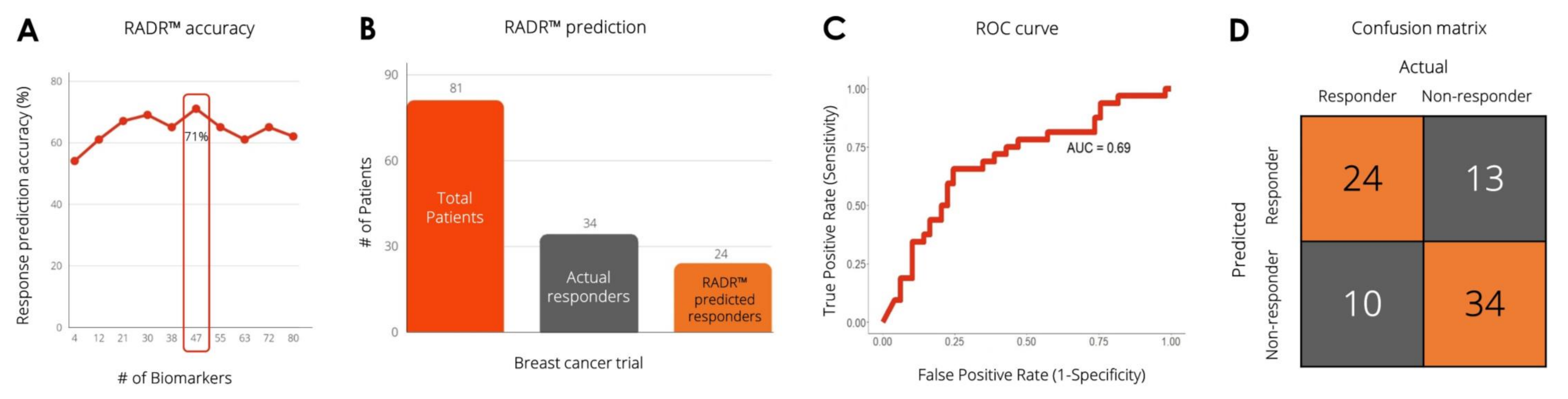
Retrospective analysis of 39 Sorafenib-treated breast cancer patients [2] was performed using RADR™. Figure 2A highlights the comparison of response prediction accuracy across a range of biomarker numbers in this clinical study. Starting from >16,000 genes, RADR™ identified a 31-gene signature in lung cancer patients as predictive of response to Sorafenib treatment with an accuracy of 83.3%. As depicted in Figure 2B, out of 30 patients included in the blinded test set, RADR™ correctly predicted 10 out of 12 actual responders (83.3% true positive rate). Figures 2C and 2D show model performance metrics such as area under curve (AUC) and confusion matrix representation, respectively. Model training was performed using an initial set of 148 genes derived from Sorafenib-lung cancer cell line data, further applied to data from 46 cell lines and 9 patients for model tuning and final gene signature development. Model testing was conducted on 30 patient records isolated as the blinded hold-out set.

Clinical Case Study 3 - Keytruda® / Melanoma


A
RADR™ accuracy
Response prediction accuracy (%)
100%
# of Biomarkers
B
RADR™ prediction
# of Patients
Total Patients
Actual responders
RADR™ predicted responders
10
5
5
Melanoma cancer trial
C
ROC curve
True Positive Rate (Sensitivity)
AUC = 0.93
False Positive Rate (1-Specificity)
D
Confusion matrix
Actual
Complete responder
Partial responder
Non responder
Predicted
Complete responder
Partial responder
Non responder
5
0
0
0
3
0
0
0
2

Retrospective analysis of 28 Pembrolizumab/ Keytruda®-treated melanoma patients [3] was performed using RADR™. Figure 3A highlights the comparison of response prediction accuracy across a range of biomarker numbers in this clinical study. Starting from >16,000 genes, RADR™ identified a 9-gene signature in melanoma patients as predictive of response to Keytruda® treatment with an accuracy of 100%. As depicted in Figure 3B, out of 10 patients included in the blinded test set, RADR™ correctly predicted all 5 out of 5 actual responders (100% true positive rate). Figures 3C and 3D show model performance metrics such as area under curve (AUC) and confusion matrix representation, respectively. Model training was performed using an initial set of 20 genes derived from 18 patients for model tuning and final gene signature development. Model testing was conducted on 10 patient records isolated as the blinded hold-out set.

Clinical Case Study 4 - Tamoxifen / Breast Cancer


A
RADR™ accuracy
Response prediction accuracy (%)
71%
# of Biomarkers
B
RADR™ prediction
# of Patients
Total Patients
Actual responders
RADR™ predicted responders
81
34
24
Breast cancer trial
C
ROC curve
True Positive Rate (Sensitivity)
AUC = 0.69
False Positive Rate (1-Specificity)
D
Confusion matrix
Actual
Responder
Non-responder
Predicted
Responder
Non-responder
24
13
10
34

Retrospective analysis of 270 Tamoxifen-treated breast cancer patients [4] was performed using RADR™. Figure 4A highlights the comparison of response prediction accuracy across a range of biomarker numbers in this clinical study. Starting from >16,000 genes, RADR™ identified a 47-gene signature in breast cancer patients as predictive of response to Tamoxifen treatment with an accuracy of 71%. As depicted in Figure 4B, out of 81 patients included in the blinded test set, RADR™ correctly predicted 24 out of 34 actual responders (70.6% true positive rate). Figures 4C and 4D show model performance metrics such as area under curve (AUC) and confusion matrix representation, respectively. Model training was performed using an initial set of 94 genes derived from Tamoxifen-breast cancer cell line data, further applied to data from 189 patients for model tuning and final gene signature development. Model testing was conducted on 81 patient records isolated as the blinded hold-out set.

Application of the RADR™ platform to real world clinical oncology datasets has accomplished external validation of the machine learning-based technology resulting in the identification of drug and tumor-type specific gene signatures predictive of response to approved cancer drugs.

Key findings and future perspectives

Case study #	Drug	Cancer indication	RADR™-derived # of drug- and cancer-specific candidate biomarkers	RADR™-derived predictive genes reported to be correlated with enhanced drug sensitivity
1	Paclitaxel	Ovarian cancer	14	FOXM1 [5], FOLR1 [6]
2	Sorafenib	Lung cancer	31	SLIT3 [7], SLC22A1 [8]
3	Keytruda®	Melanoma	9	None published
4	Tamoxifen	Breast cancer	55	PGR [9]

- Lantern Pharma's RADR™ platform has been validated on approximately 1000 patient records from real world clinical oncology evidence, with greater than 80% average response prediction accuracy.
- If RADR™ is employed to initiate biomarker-driven clinical trials involving the drugs from the currently presented case studies, the response rates for patients is expected to significantly improve.
- RADR™-driven drug response predictions are capable of improving trial outcomes by recruiting expected responders and reducing contraindicated patient selection.
- RADR™ will serve as a potent and accelerated *in silico* approach complementing in vitro wet laboratory techniques while determining patient eligibility for a particular cancer therapy.

References

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[8] Herraez et al., Expression of SLC22A1 Variants May Affect the Response of Hepatocellular Carcinoma and Cholangiocarcinoma to Sorafenib. Hepatology (2013)
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