

ET-16

From Manual to Machine: Leveraging Best-of-Breed Approaches in Clinical Data Management

Joe Lebers, Product Manager

Christina Dinger, Sr. Director of Product & Marketing



Joe Lebers

Product Manager,
ThoughtSphere

joe.lebers@thoughtsphere.com

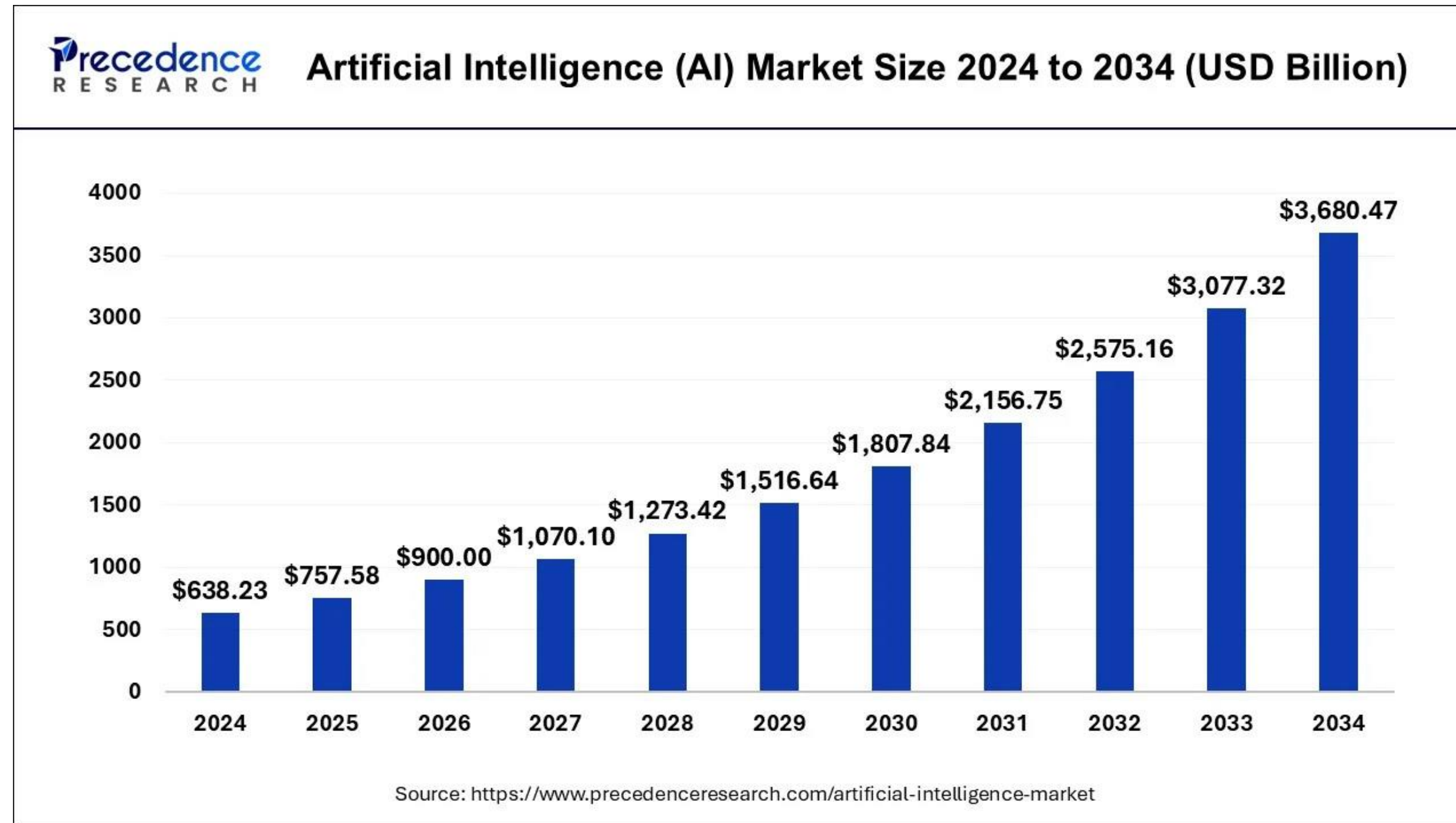


Christina Dinger

Senior Director, Product,
ThoughtSphere

christina.dinger@thoughtsphere.com

AI in Society and Business Expected to grow by~6x, by 2034.



Source: <https://www.precedenceresearch.com/artificial-intelligence-market>

Healthcare and Clinical Trials are no Exception

2020

Key indicators of phase transition for clinical trials through machine learning

Felipe Feijoo ¹  , Michele Palopoli ², Jen Bernstein ³, Sauleh Siddiqui ^{4 5}, Tenley E. Albright ⁶

Source: <https://www.nature.com/articles/s41746-021-00505-5>

Machine learning model to predict oncologic outcomes for drugs in randomized clinical trials

Alexander V. Schperberg, Amélie Boichard, Igor F. Tsigelny, Stéphane B. Richard, Razelle Kurzrock 

Source: <https://www.nature.com/articles/s41746-021-00505-5>

2021

Utilizing machine learning to improve clinical trial design for acute respiratory distress syndrome

[E. Schwager](#), [K. Jansson](#), [A. Rahman](#), [S. Schiffer](#), [Y. Chang](#), [G. Boverman](#), [B. Gross](#), [M. Xu-Wilson](#), [P. Boehme](#), [H. Truebel](#)  & [J. J. Frassica](#) 

Source: <https://www.nature.com/articles/s41746-021-00505-5>

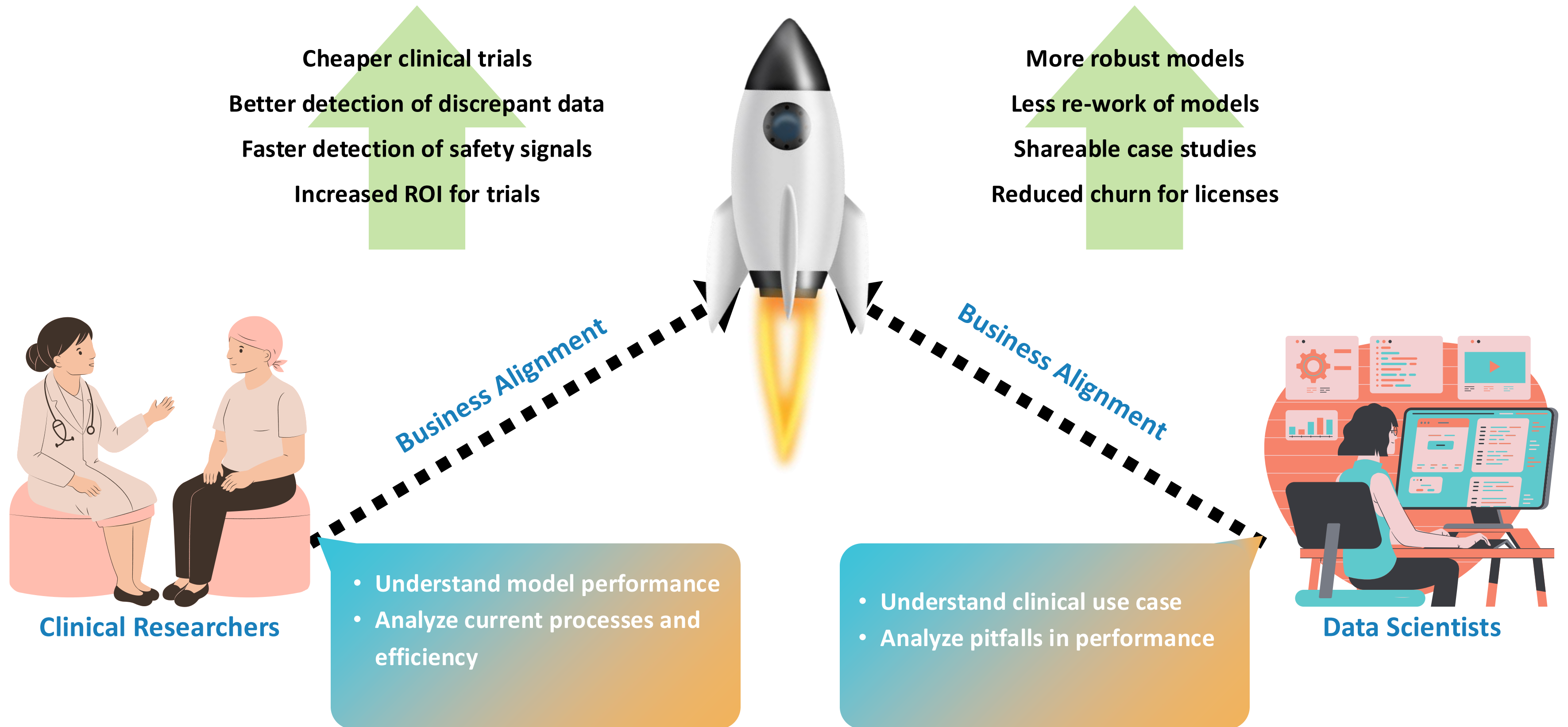
2024

Machine Learning in Modeling Disease Trajectory and Treatment Outcomes: An Emerging Enabler for Model-Informed Precision Medicine

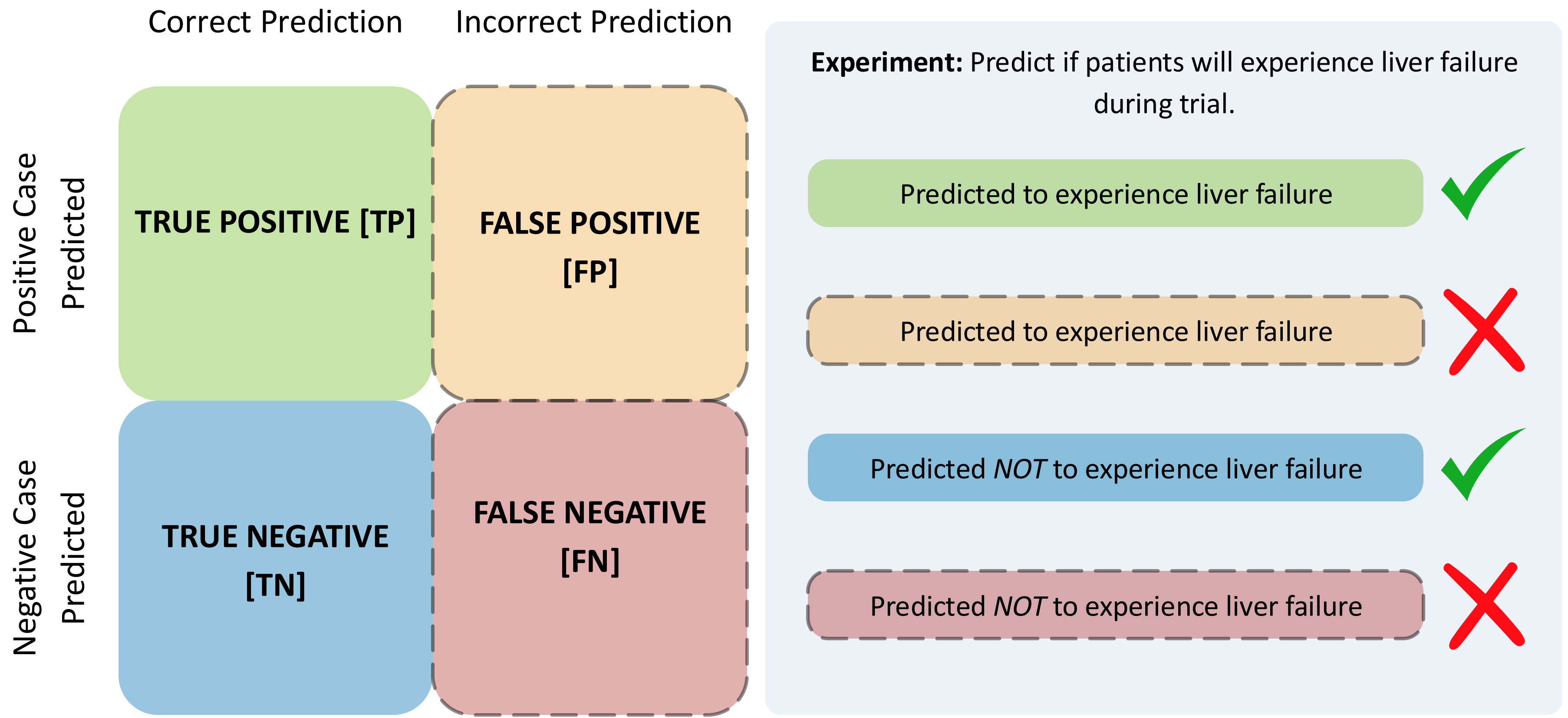
Nadia Terranova , Karthik Venkatakrishnan 

Source: <https://www.nature.com/articles/s41746-021-00505-5>

Alignment Between Research Orgs and Software Vendors



Machine Learning Confusion Matrix



Penalty Differences in Classes

		Correct Prediction	Incorrect Prediction
Positive Case	Predicted	TRUE POSITIVE [TP]	FALSE POSITIVE [FP]
	Predicted	TRUE NEGATIVE [TN]	FALSE NEGATIVE [FN]

Missing Positives can be detrimental:

- Can result in patient death or harm
- At a higher-level, jeopardize safety of the study

Recall / Sensitivity =

$$\frac{\text{TP}}{\text{TP} + \text{FN}}$$

Benchmarks if we can catch all at-risk patients.

Penalty Differences in Classes

		Correct Prediction	Incorrect Prediction
Positive Case	Predicted	TRUE POSITIVE [TP]	FALSE POSITIVE [FP]
	Predicted	TRUE NEGATIVE [TN]	FALSE NEGATIVE [FN]

Too many False Positives can impede efficiency:

- Could have been faster to find through human-led review

Precision =

$$\frac{\text{TP}}{\text{TP} + \text{FP}}$$

Benchmarks the reliability of Positive predictions.

Issues with Accuracy

		Correct Prediction	Incorrect Prediction
Predicted	Positive Case	TRUE POSITIVE [TP]	FALSE POSITIVE [FP]
	Negative Case	TRUE NEGATIVE [TN]	FALSE NEGATIVE [FN]

Accuracy measures the correct rate of the model.

Accuracy =

$$\frac{\text{TP} + \text{TN}}{\text{TP} + \text{TN} + \text{FP} + \text{FN}}$$

When the frequency of cases are imbalanced, accuracy measures can lack value.

Issues with Accuracy

		Correct Prediction	Incorrect Prediction
Predicted	Positive Case	TRUE POSITIVE [TP] 1	FALSE POSITIVE [FP] 3
	Negative Case	TRUE NEGATIVE [TN] 87	FALSE NEGATIVE [FN] 9

Accuracy measures the correct rate of the model.

Accuracy =

$$\frac{1 + 87}{1 + 87 + 3 + 9}$$

When the frequency of cases are imbalanced, accuracy measures can lack value.

88% Accuracy

Issues with Accuracy

Accuracy =

$$\frac{1 + 87}{1 + 87 + 3 + 9}$$

88% Accuracy



This model fails to predict the patients at-risk for liver failure, which is a severe error!

Recall =

$$\frac{TP}{TP + FN}$$

$$\frac{1}{1 + 9}$$

10% Recall



Tweaking the Positive Prediction Tolerance can catch more True Positives...

Accuracy =

$$\frac{6 + 80}{6 + 70 + 20 + 4}$$

= 86% Accuracy

Recall =

$$\frac{6}{6 + 4}$$

= 60% Recall

Improved power to
detect Positive cases!

Precision =

$$\frac{6}{6 + 20}$$

= 23.1% Precision

However, more False
Positives.

In Practice, False Positives can Impede Efficiency

Experiment: Predict if patients will experience liver failure during trial.

Considerations: Patients that will potentially experience liver failure, should have additional panels performed and a Medical Monitor to verify their safety.

Costs:

- Medical Monitor vs Data Manager pay differential.
- Require at-risk patients to visit for blood drawing.
- Cost to perform the additional liver panel.
- Time delay due to this additional analysis.

The costs are highly dependent on safety protocols, experience and skills of the data management team, and required procedures.

Following False Positives by the model can increase costs in time, resources, money, and attention toward other patients. Team benchmarking is needed.

In Practice, False Positives can Impede Efficiency

Exercise: As a Data Management Function Head, deeply understand your team's productivity to determine if the ML solution will improve productivity and progress to business objectives.

User Benchmarking: Sit with the data management team to understand their strengths, SLAs, and weaknesses.

Benchmark by Model Performance: Apply the model performance metrics in the same analysis to establish an "AFTER" for the implementation.

Pilots Give Better Insight: Perform the same user benchmarking, but with the ML solution applied to real data, used by the real team.

Calculate Risk/Value Metric and Compare. There are different risk analyses but for this example we will calculate *Risk* and *Expected Value*

Example: Model the Risk and Estimate Value

Activity	Outcome	Uncertainty	Value
Find issue in listing review	Query	-0.20	8min
	No Query	0.80	10min
Find issue in data check output	Query	-0.90	4min
	No Query	0.10	6min
Find issue Positive Predictions	Query	-0.70	4min
	No Query	0.30	5min
Find issue Negative Predictions	Query	-0.20	6min
	No Query	0.80	7min

Hypothesis: Is $ROCII^* > ROI$?

$$Risk = (Uncertainty) \times (Value \text{ of Cases})$$

$$Risk_{Total} = \sum P(X_i) \times X_i$$

**Return on Competitive Intelligence Investment

Query represents reduction in risk

No Query represents increase in risk

Example: Model the Risk and Estimate Value

Activity	Outcome	Uncertainty	Value
Find issue in listing review	Query	-0.20	8min
	No Query	0.80	10min
Find issue in data check output	Query	-0.90	4min
	No Query	0.10	6min
Find issue Positive Predictions	Query	-0.70	4min
	No Query	0.30	5min
Find issue Negative Predictions	Query	-0.20	6min
	No Query	0.80	7min

EXPECTED RISK TO VALUE =

Hypothesis: Is $ROCI^* > ROI$?

Risk = (Uncertainty) × (Value of Cases)

$Risk_{Total} = \sum P(X_i) \times X_i$

**Return on Competitive Intelligence Investment

BEFORE	AFTER
-0.20(8)	-0.70(4)
0.80(10) +	0.30(5) +
-0.90(4) +	-0.20(6) +
0.10(6) +	0.80(7) +
3.4	3.1

3.4

[Cost of DM/min]

>

3.1

[Cost of DM/min]

Future Directions

Sponsors should come ready with:

- A fundamental understanding of True Positives, False Positives (etc.) and performance metrics.
- A baseline model of efficiency for the target DM team.
- Incorporating RBCDM and blended approaches.

Vendors should be ready to:

- Explain model performance metrics to business users in the context of business case.
- Tweak model performance based on sponsor, with explainability.
- Be open to blended approach by sponsor.

For the industry:

- Implementing ML should be treated as a blended data science, safety, and human resource issue.
- Pilots should be more commonplace because organizations differ.
- More regulatory guidance from FDA will help standardize analyses.