ScreenMCM: A Machine Learning-Based Product Screening Tool to Accelerate Medical Countermeasure Development

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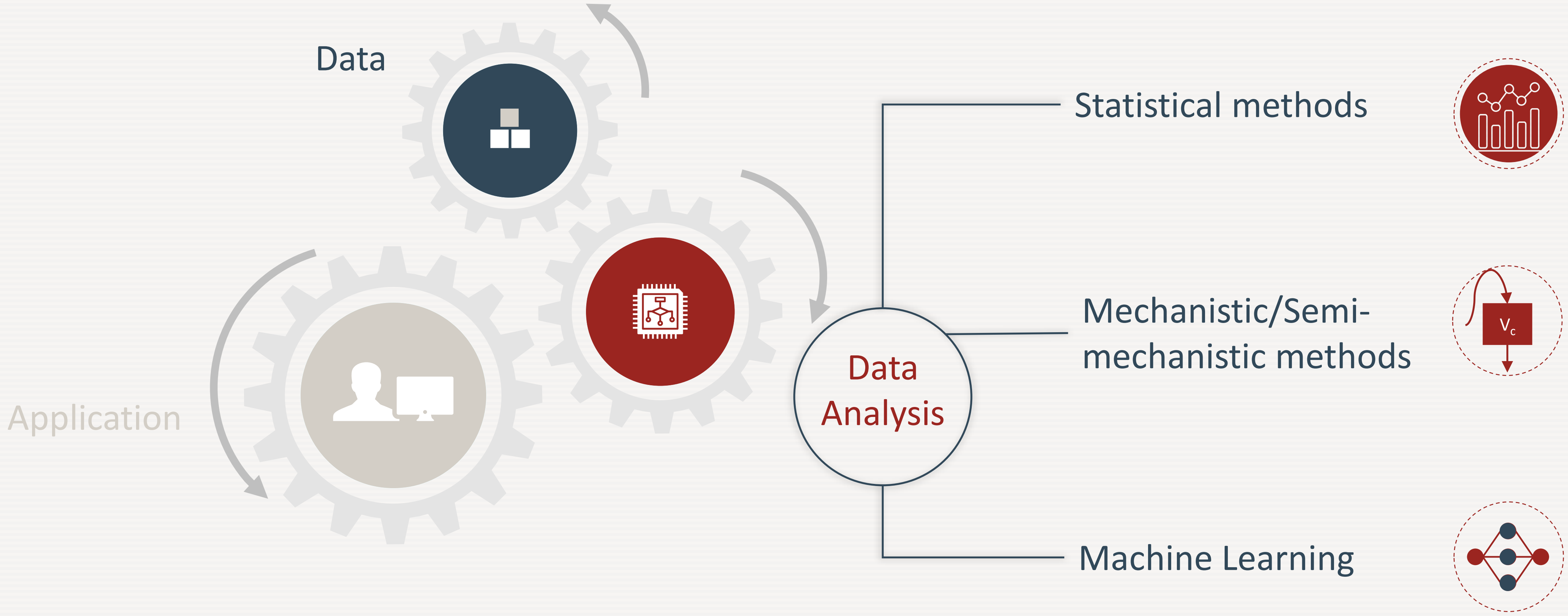
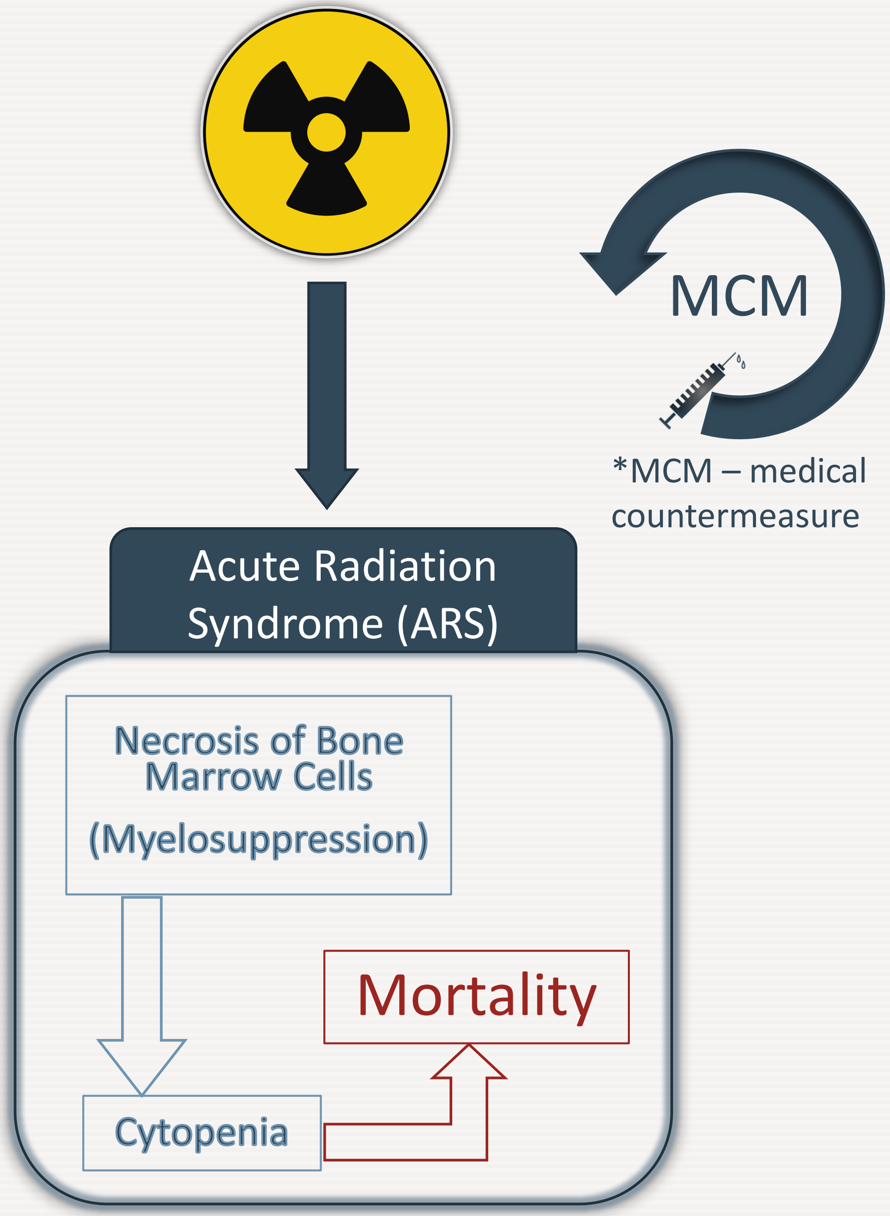
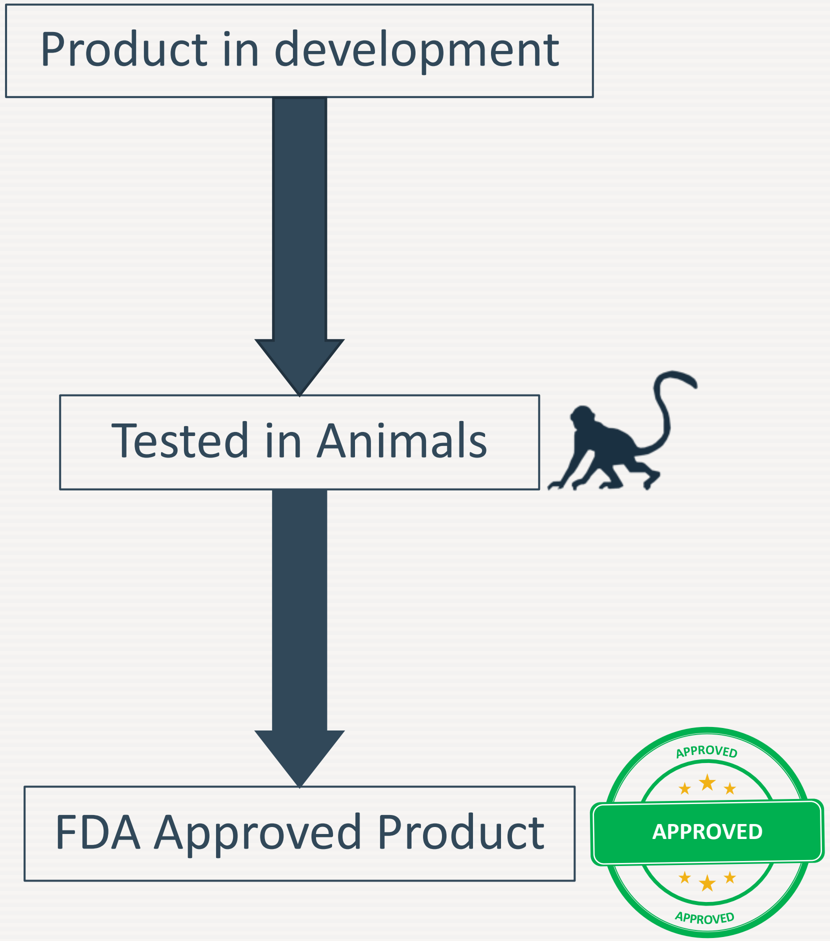
ML is a New Tool for the Advancement of Precision Medicine



Jarugula et al. *The Journal of Clinical Pharmacology*; 2021

MCMs treat ARS and are Approved by US-FDA after Animal Testing



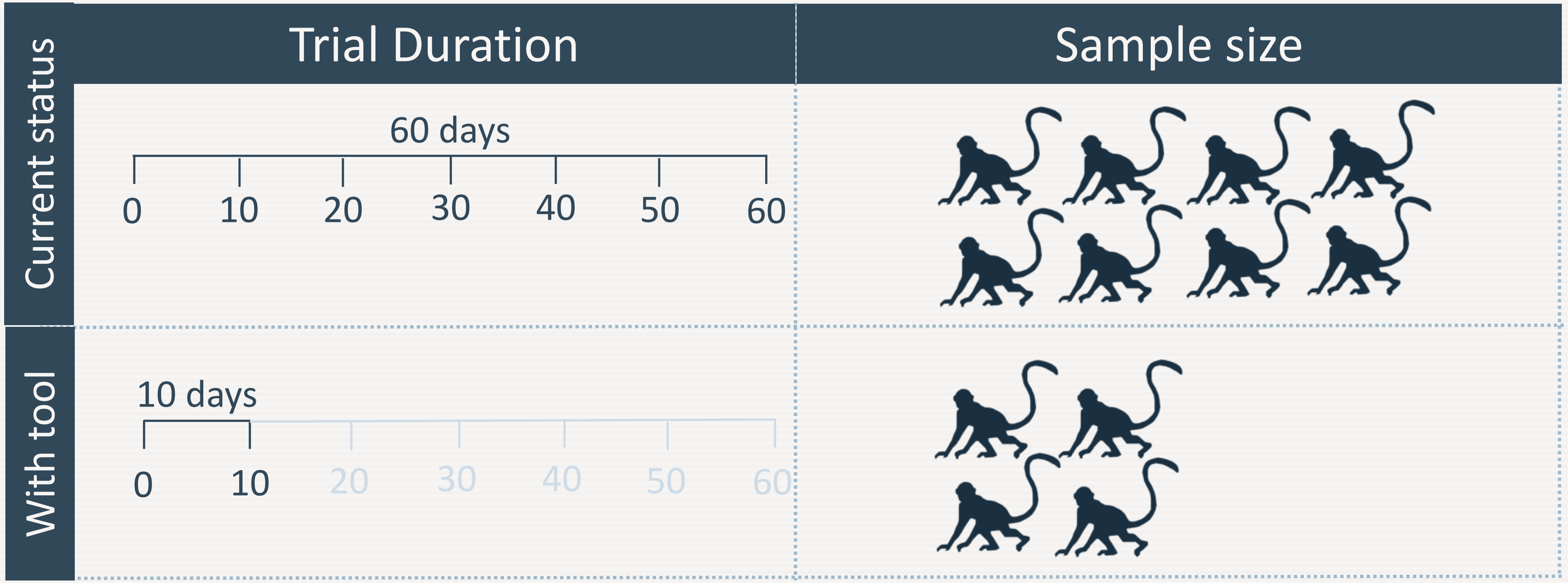


https://www.fda.gov/emergency-preparedness-and-response/mcm-regulatory-science/animal-rule-information

Failure Rate

75%

ScreenMCM Accelerates Product Screening



<u>FDA Modernization Act 2.0:</u> This bill authorizes the use of certain alternatives to animal testing, including cell-based assays and **computer models**, to obtain an exemption from the US-FDA to investigate the safety and **effectiveness of a drug**

https://www.congress.gov/bill/117th-congress/senate-bill/5002

ScreenMCM Was Built by Pooling Existing Data

BIG DATA

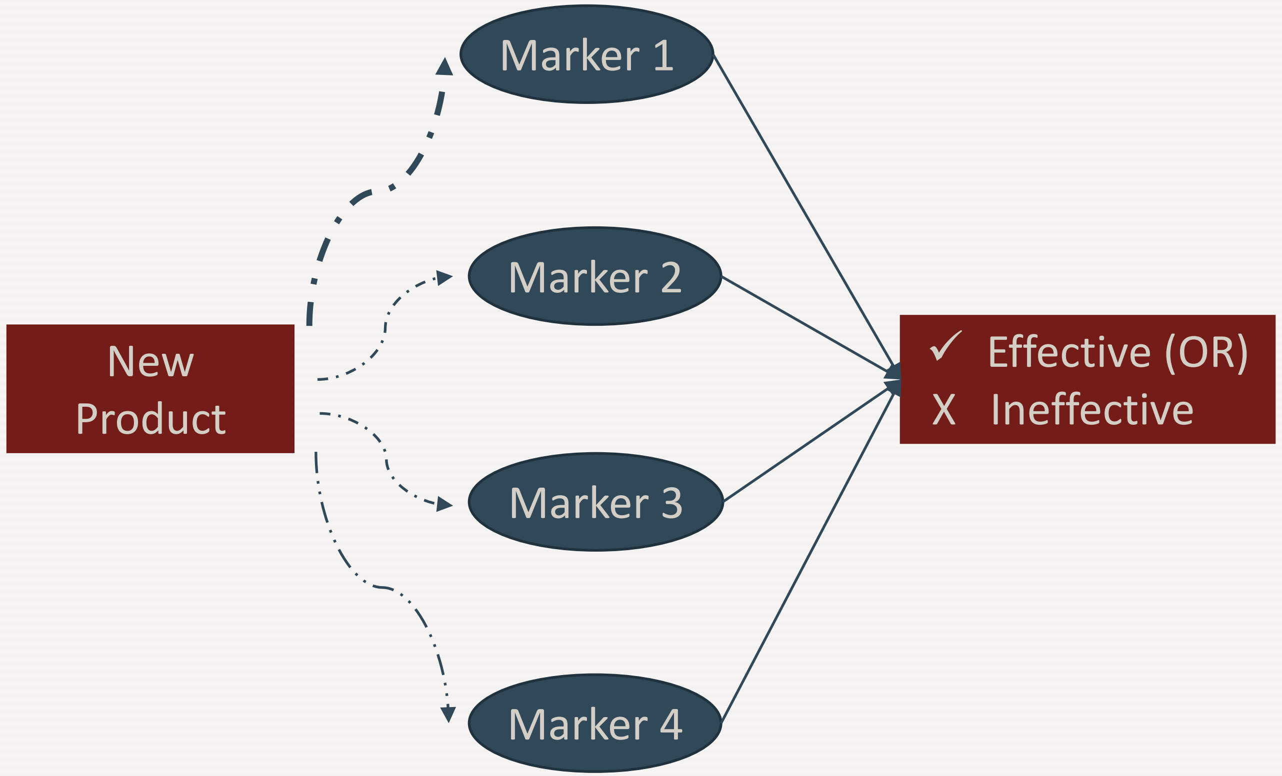
01 3 studies

02 501 non-human primates

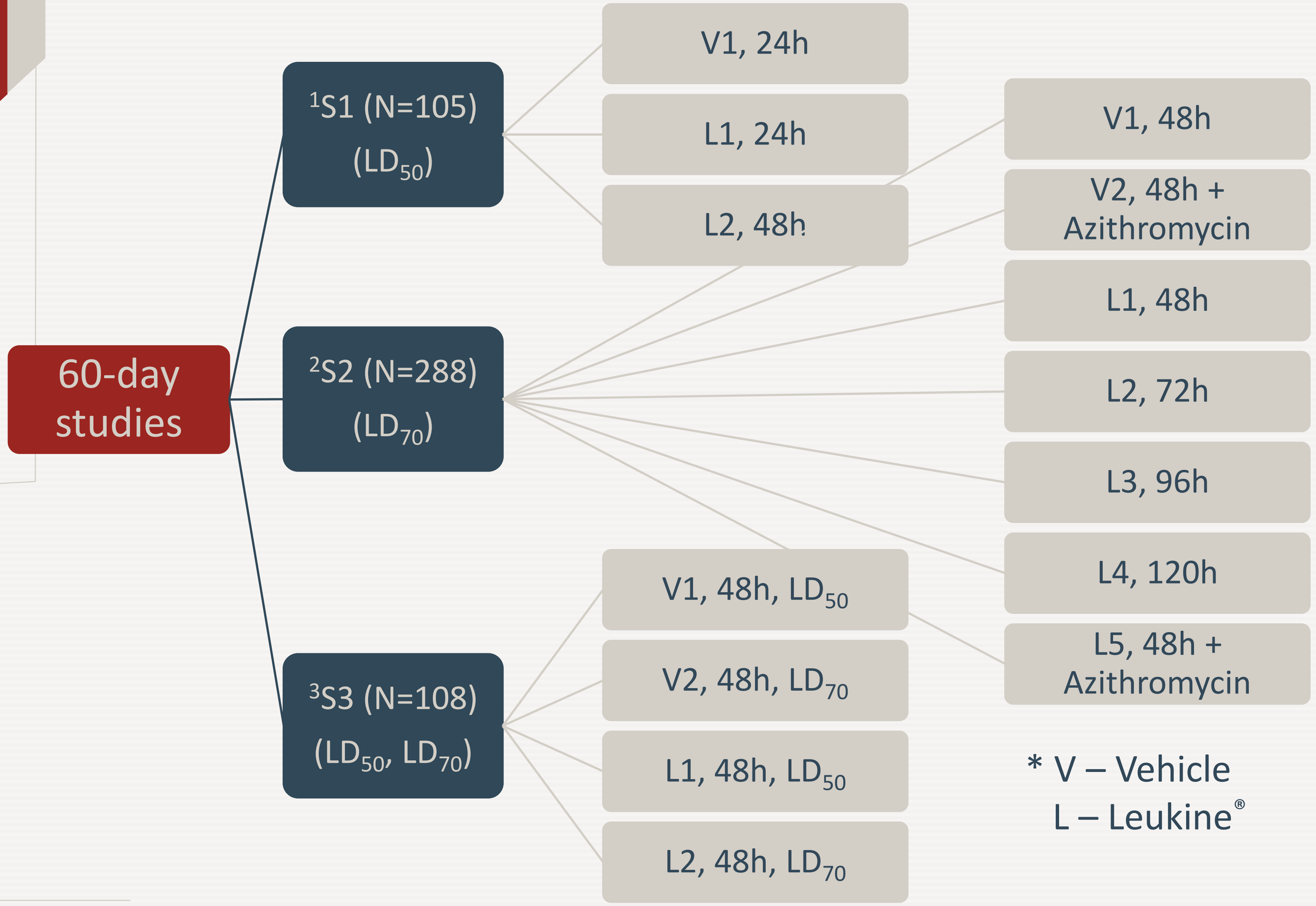
03 12 biomarkers

04 Daily data for 60 days

05 5 radiation doses



Study Designs and Data



* V – Vehicle
L – Leukine®

12 Biomarkers

- RBC, HGB, HCT, RETI, PLAT
- WBC, ANC, ALC, MONO, LGUNSCE, BASO, EOS

Blood sampling times

- 1-30 days – Daily
- 31-60 days – Every 3 days

Animals

- 501
- ~15k rows of data

[1]*Final Study Report, Study14-045 Lovelace Biomedical Research Institute, Doyle-Eisele M, et al*
[2]*Final Study Report, Study TSK-0144 CiToxLabs, Ascah A, et. al.* [3]*Final Study Report Study 1017-3493, CitTox Labs, Pouliot M, et. al.*

3 studies – 60 days each | **501 animals** | **12 biomarkers** | **Longitudinal measurements**

Workflow to Predict Mortality due to ARS Using Supervised Machine Learning

01 Data Preparation

- ✓ Data from a time frame
- ✓ Predictors : Raw levels and/or aggregation of time windows

  Outcome : 60-day mortality

02 Train-test split

60% Training

40% Testing

03 Model Fitting

Elastic-net regression, XGBoost, Support vector machines, Random forest

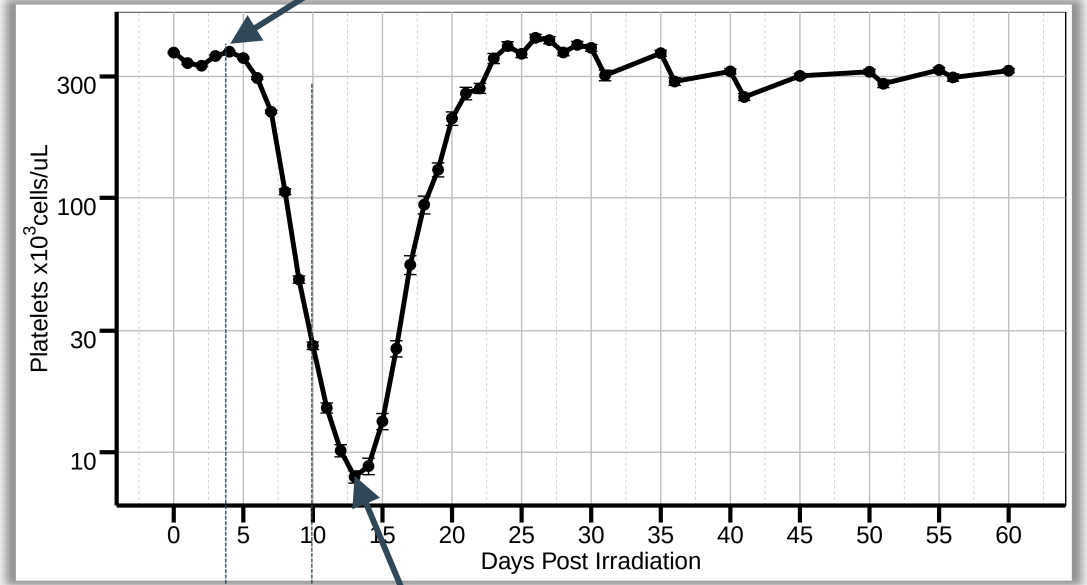
04 Qualification

- ✓ ROC-AUC
- ✓ Accuracy
- ✓ Calibration Plot
- ✓ Spiegelhalter Z-test

05 Prediction performance

Time Frame Selection and Data Preparation

Depletion starts – Day 4

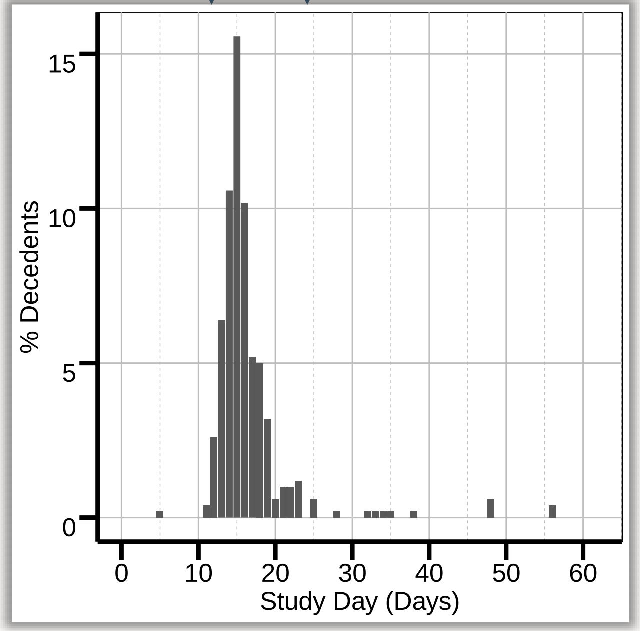


Line is shown for mean ± standard error of the mean

4-10 days

Recovery starts – Day 13

95% Deaths in Days 12-24



Time window aggregation metrics

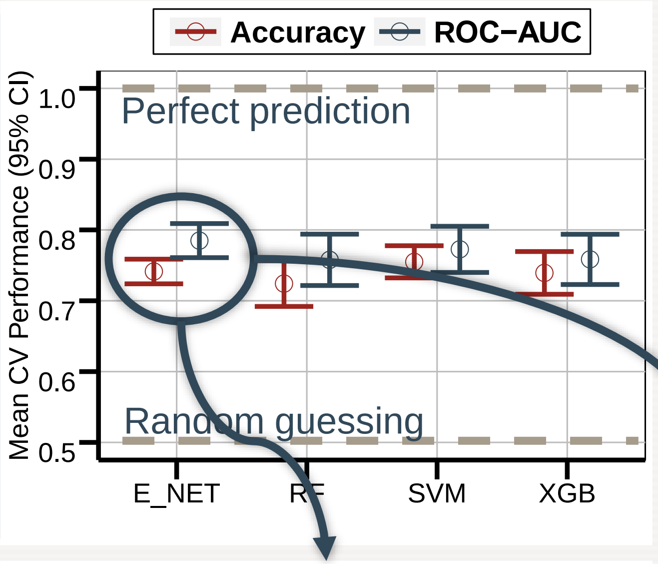
- ✓ Area under curve
- ✓ Slope
- ✓ Maximum
- ✓ Minimum
- ✓ Mean
- ✓ Auto-correlation
- ✓ Change from baseline
- ✓ Daily biomarker levels

Final dataset

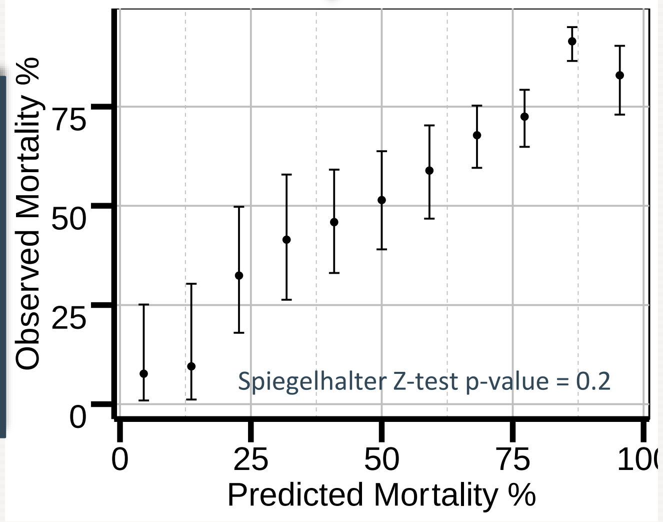
500 animals x
136 predictors

Elastic-net regression algorithm performed similar to other algorithms based on ROC-AUC & Accuracy

Grid-search CV Results

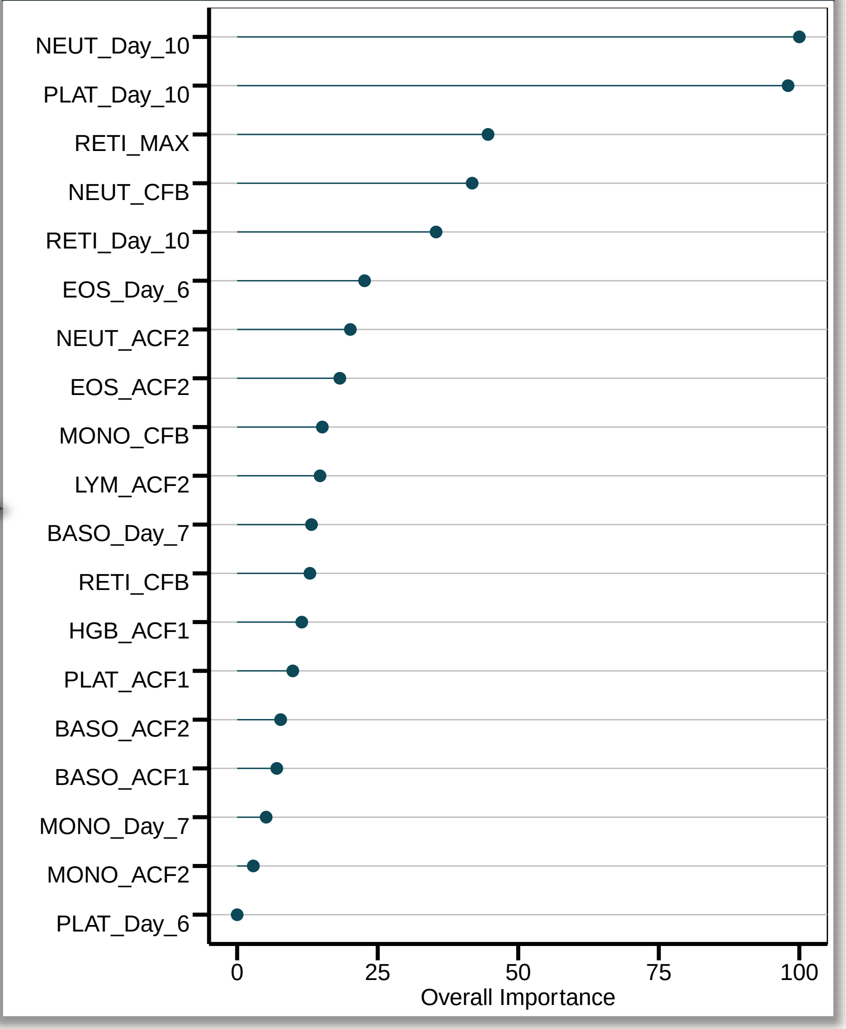


Calibration Plot



+ Recursive feature elimination

Predictor Importance



E_NET: Elastic-net regression; RF – random forest; SVM – support vector machine; XGB - XGBoost

CFB – change from baseline, ACFn – auto-correlation factor with lag of n days, MIN – minimum, MAX - maximum

Final Elastic-net Regression Model Provides Greater than 70% Accuracy and ROC-AUC on the Test (Unseen) Dataset

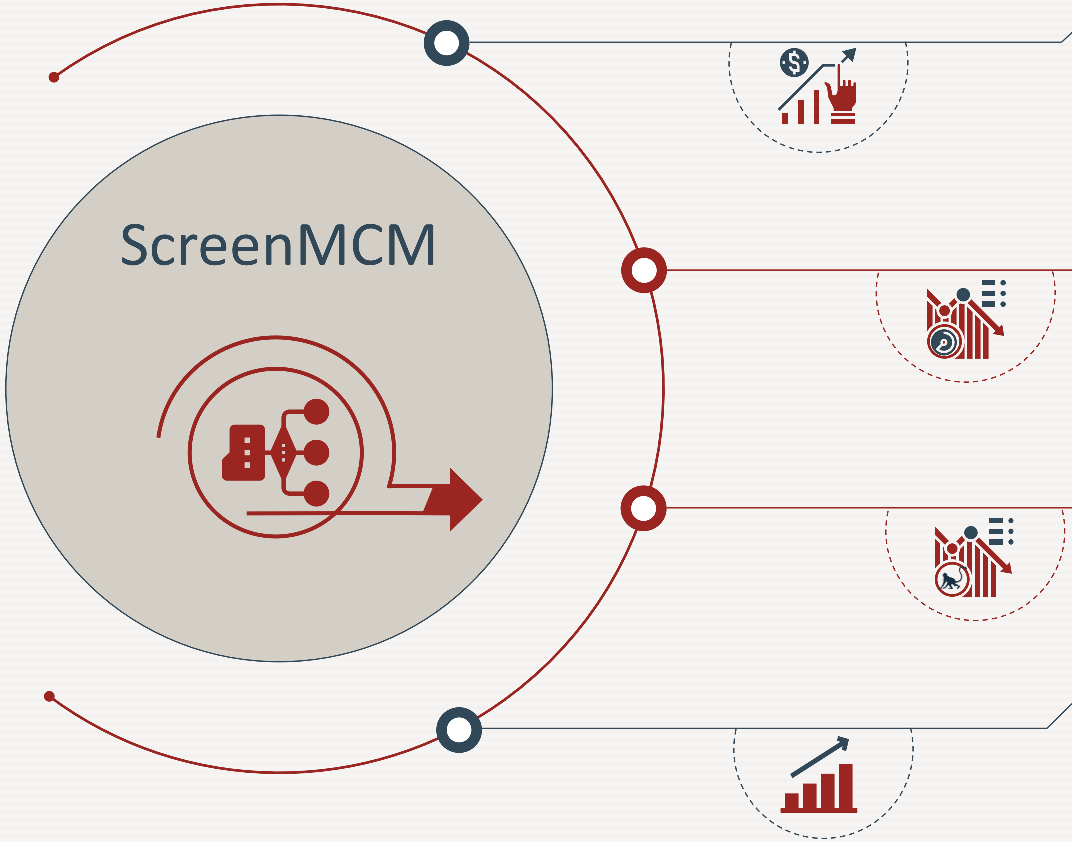
Metric	Value[1]	95% CI[2]
Accuracy	**0.71**	(0.66, 0.77)
ROC-AUC	**0.75**	(0.67, 0.81)
Balanced Accuracy	0.63	(0.57, 0.7)
F1 Score	0.80	(0.77, 0.84)
MCC[3]	0.31	(0.17, 0.46)
NPV[4]	0.63	(0.51, 0.77)
PPV[5]	0.73	(0.7, 0.78)

[1]Value refers to test performance on the test dataset
[2]95% CI was obtained using 2000 bootstraps on the test dataset
[3]Matthew's Correlation Coefficient
[4]Negative Predictive Value
[5]Positive Predictive Value

Application of ScreenMCM

Products in pipeline	*Hypothetical treatment effect on platelets*	Placebo survival rate	ScreenMCM	Treatment survival rate
Product 1	*No effect*			23%
Product 2	*10%*	23%		23%
Product 3	*50%*			40%
Product 4	*100%*			47%

Conclusions



- Increased probability of trial success
- Shorten product development time
- Reduced animal testing
- Continuous process improvement

Machine Learning is Being Expanded Across Therapeutic Areas to Achieve the Goal of Precision Medicine

Individualized treatment planning for lung cancer


Volume 25, Issue 14
15 July 2019

Clinical Cancer Research

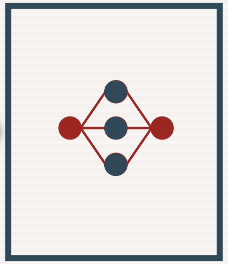
PRECISION MEDICINE AND IMAGING | JULY 15 2019

Machine Learning to Build and Validate a Model for Radiation Pneumonitis Prediction in Patients with Non–Small Cell Lung Cancer FREE

Hao Yu; Huanmei Wu; Weili Wang; Shruti Jolly; Jian-Yue Jin; Chen Hu; Feng-Ming (Spring) Kong

Input

Inflammatory cytokines
Patient characteristics
Treatment plan



Output

Radiation toxicity (pneumonitis)

Biomarker identification for immunotherapy

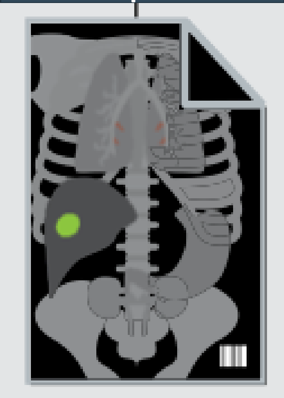

THE LANCET
Oncology

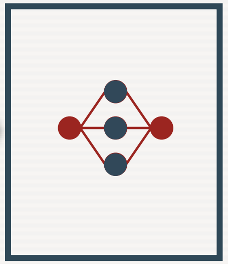
ARTICLES | VOLUME 19, ISSUE 9, P1180-1191, SEPTEMBER 2018

A radiomics approach to assess tumour-infiltrating CD8 cells and response to anti-PD-1 or anti-PD-L1 immunotherapy: an imaging biomarker, retrospective multicohort study

Roger Sun, MD • Elaine Johanna Limkin, MD • Maria Vakalopoulou, PhD • Laurent Dercle, MD • Stéphane Champiat, MD • Shan Rong Han, MD • et al. Show all authors • Show footnotes

Input





Output

CD8 cell penetration & treatment response

Acknowledgments & Conflicts of Interest

- Partner Therapeutics, Inc. is the project sponsor.
- Data used in this analysis was generated in three NHP studies supporting Leukine®'s FDA-approval as a MCM to treat Acute Radiation Syndrome which were funded by the Office of the Assistant Secretary for Preparedness and Response (ASPR), Biomedical Advanced Research and Development Authority (BARDA), under Contract number HHSO1002013000051.
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  - John L. McManus, Partner Therapeutics

Thank You