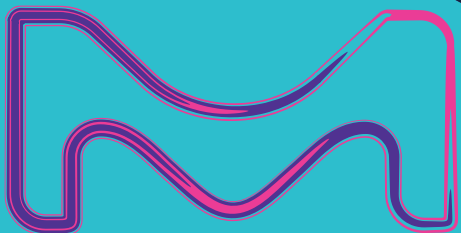


AI/ML-enabled drug-disease modeling

Enabling model-informed precision medicine
with Artificial Intelligence and Machine Learning

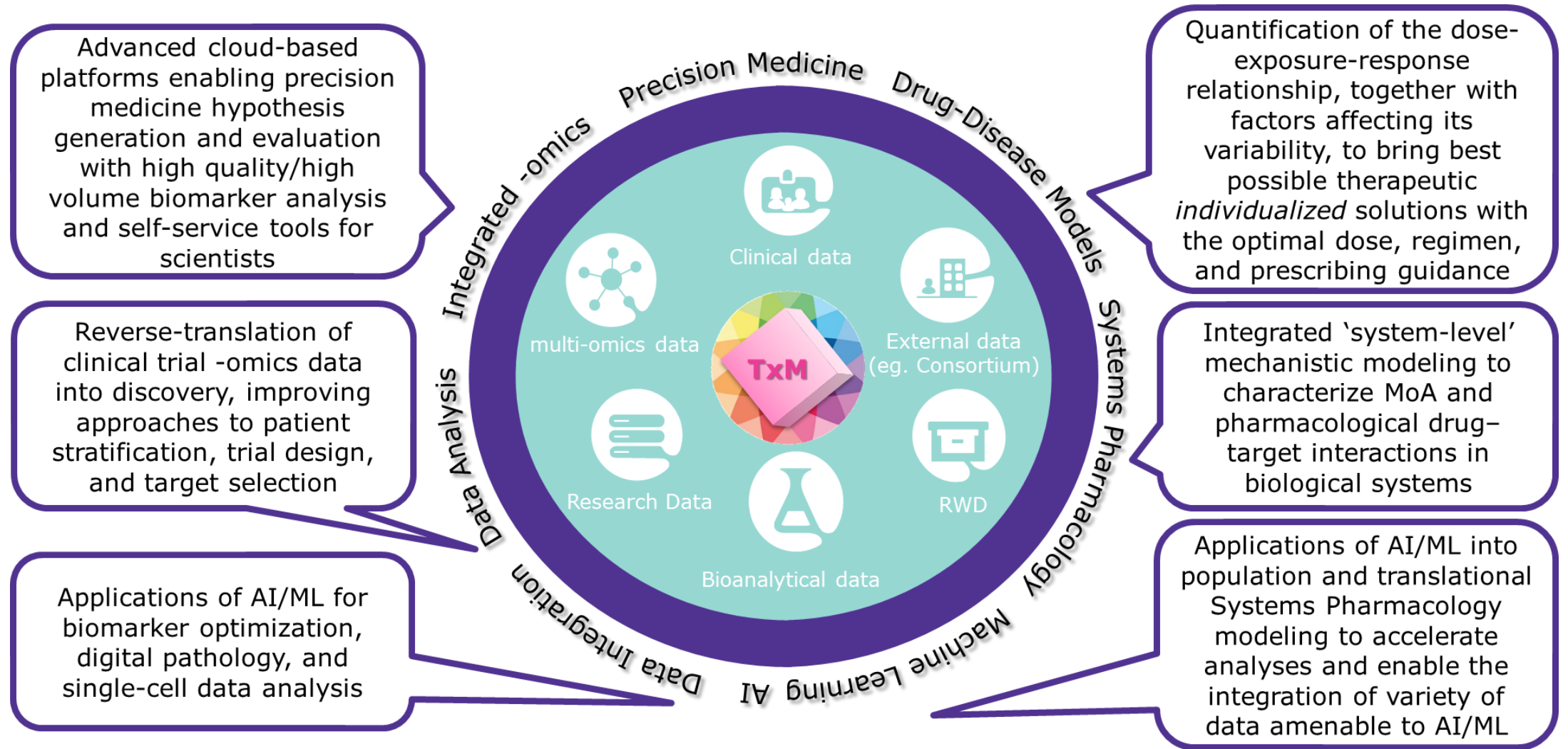


Nadia Terranova, PhD
Quantitative Pharmacology



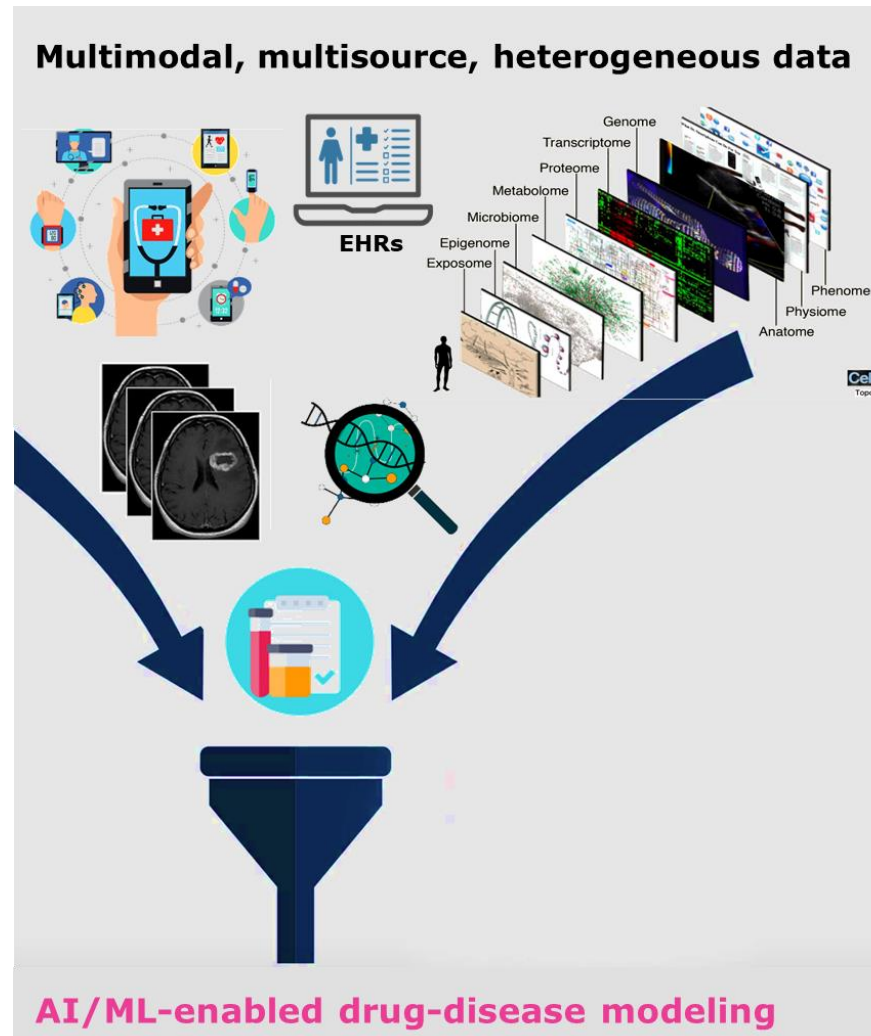
Advanced Analytics are a strategic Enabler of Translational Precision Medicine

Patient-centered forward and reverse translation



Source: Terranova, N., Venkatakrishnan, K., & Benincosa, L. J. *The AAPS Journal*, 2021

AI/ML-enabled drug-disease modeling leverage high-dimensional data Towards Model-Informed Precision Medicine 2.0



AI/ML offer opportunities to advance understanding of disease and drug MoA with a totality of evidence mindset

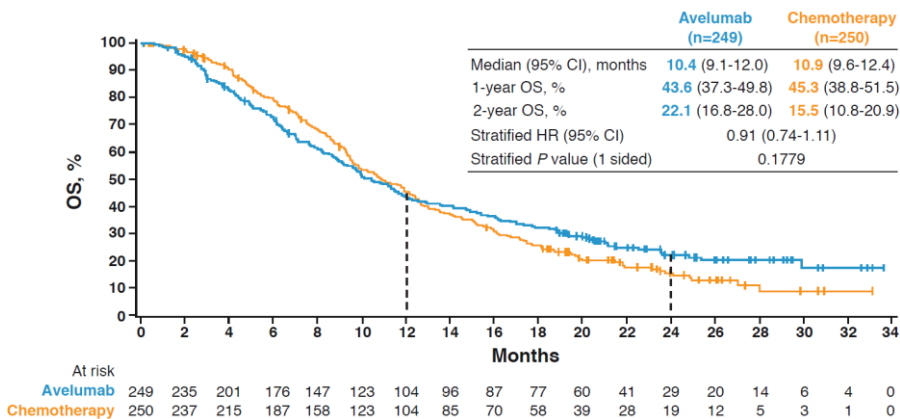
- Maximizing knowledge of **sources of variability** in drug exposure and response
- Identifying **ML-derived metrics or signatures** related to disease evolution
- Forecasting of disease progression in “**mechanism-agnostic**” manner

MoA: mechanism of action

ML-based identification of prognostic and predictive factors of long-term overall survival and tumor growth dynamics

Avelumab JAVELIN Gastric trial

Superior survival prior to 12 months for chemotherapy continuation arms and better long-term survival for maintenance avelumab arm



Is there a subpopulation that could benefit from avelumab?



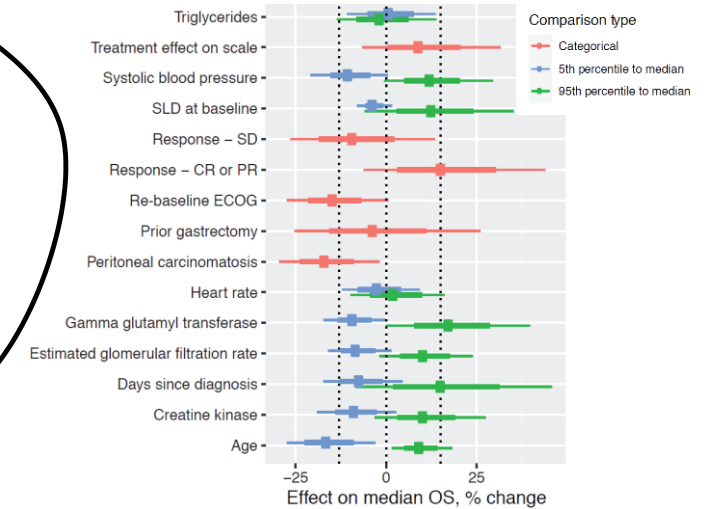
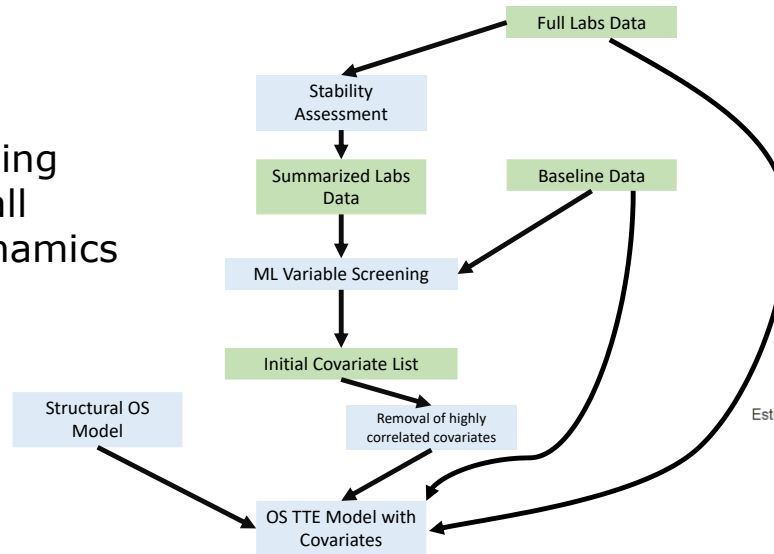
- Parametric **time-to-event** modeling for **OS**
- Modeling of **tumor growth dynamics**
- Identification of prognostic and predictive factors informed by ML

N. Terranova, J. French, H. Dai, M. Wiens,... & K. Venkatakrishnan. *Pharmacometric modeling and machine learning analyses of prognostic and predictive factors in the JAVELIN Gastric 100 phase III trial of avelumab*. CPT: PSP 2022

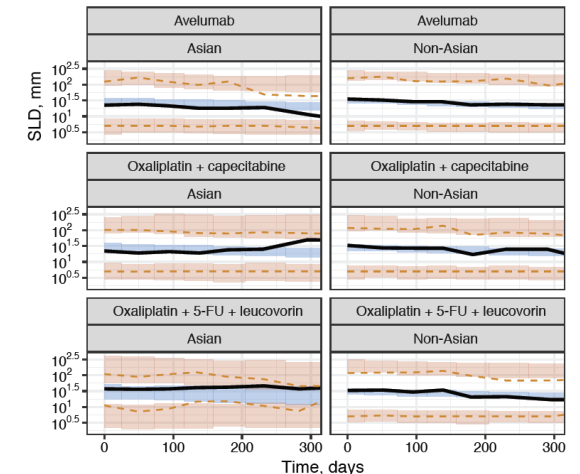
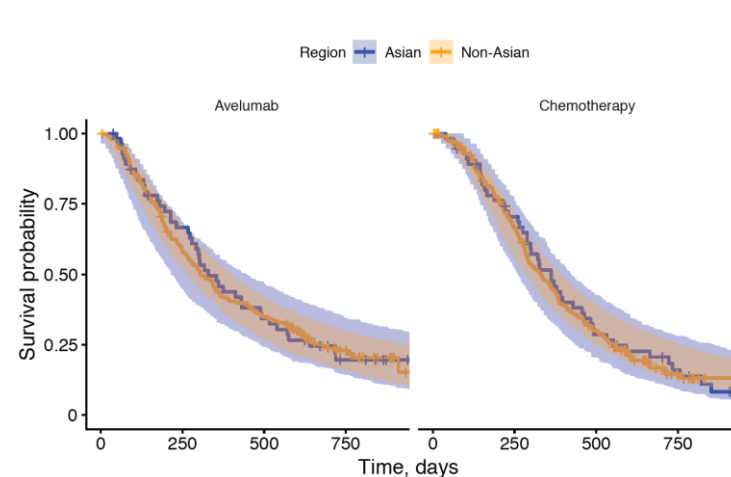
OS: Overall Survival; TGD: Tumor Growth Dynamics

Disease models of OS and tumor growth dynamics were developed by integrating time-invariant and time-varying covariates informed by ML

ML was used to assess baseline and time-varying **prognostic and predictive factors** for overall survival (89 covariates) and tumor growth dynamics (52 covariates)



Lack of discernable differences in disease progression or outcomes between Asian and non-Asian populations

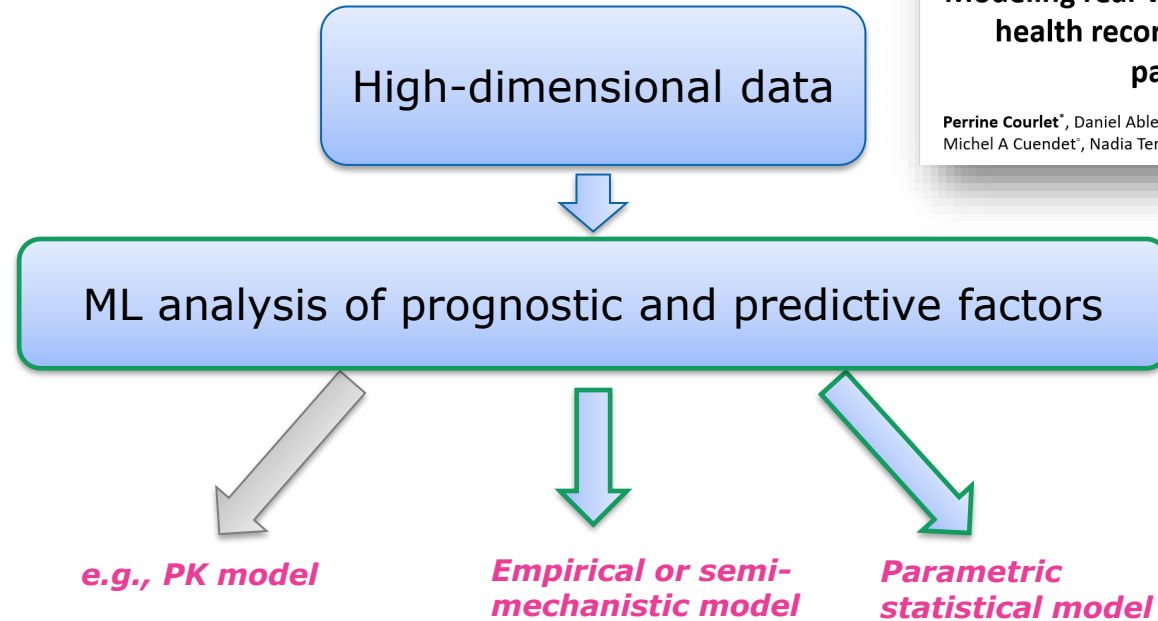


OS: Overall Survival; TGD: Tumor Growth Dynamics

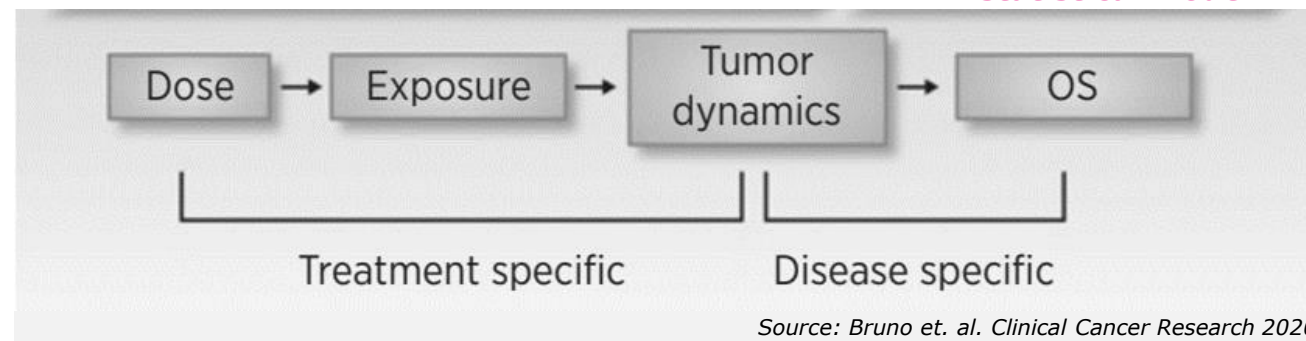
Terranova et. al. CPT: PSP 2022

ML assessments of sources of variability well integrate large data and novel biomarkers

Advancing model-informed precision oncology



Tumor Size-Overall Survival:
Current Paradigm

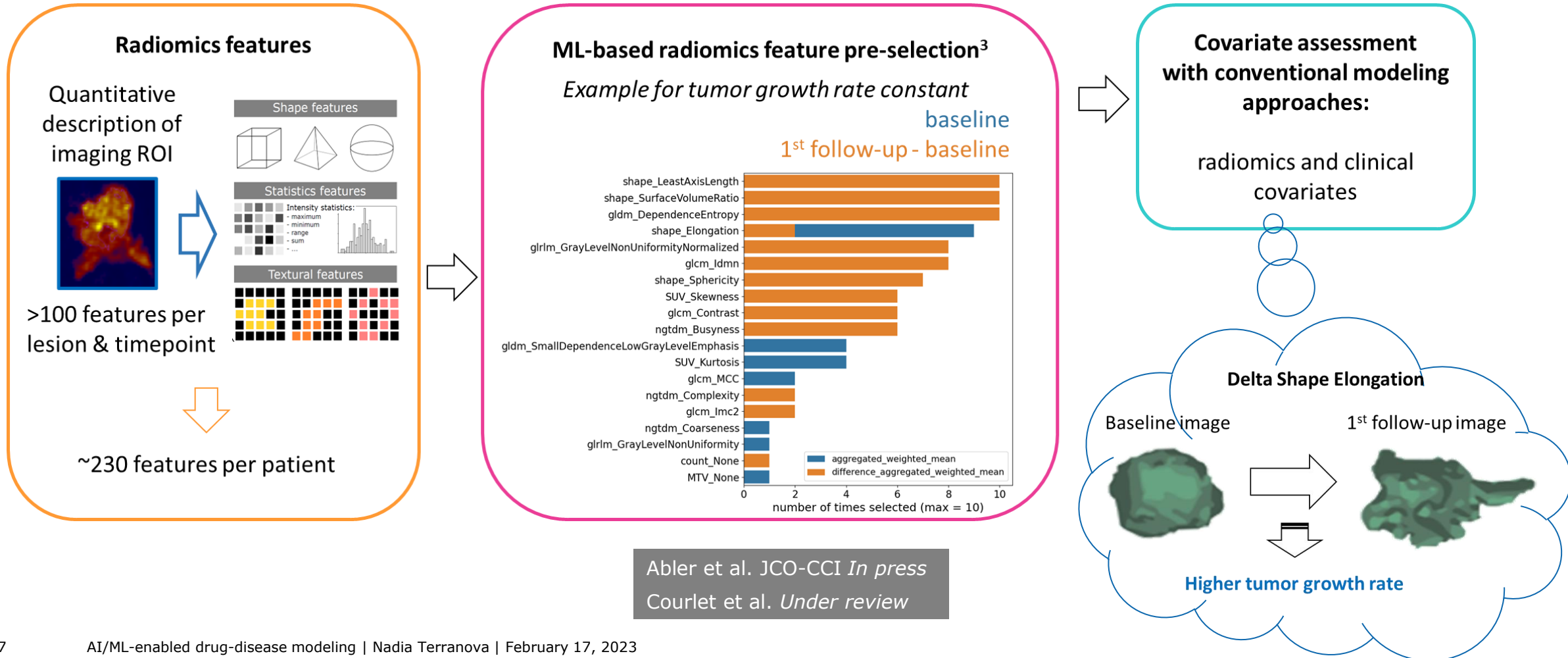


Source: Bruno et. al. Clinical Cancer Research 2020

Tumor phenotype features can inform tumor growth dynamics and progression

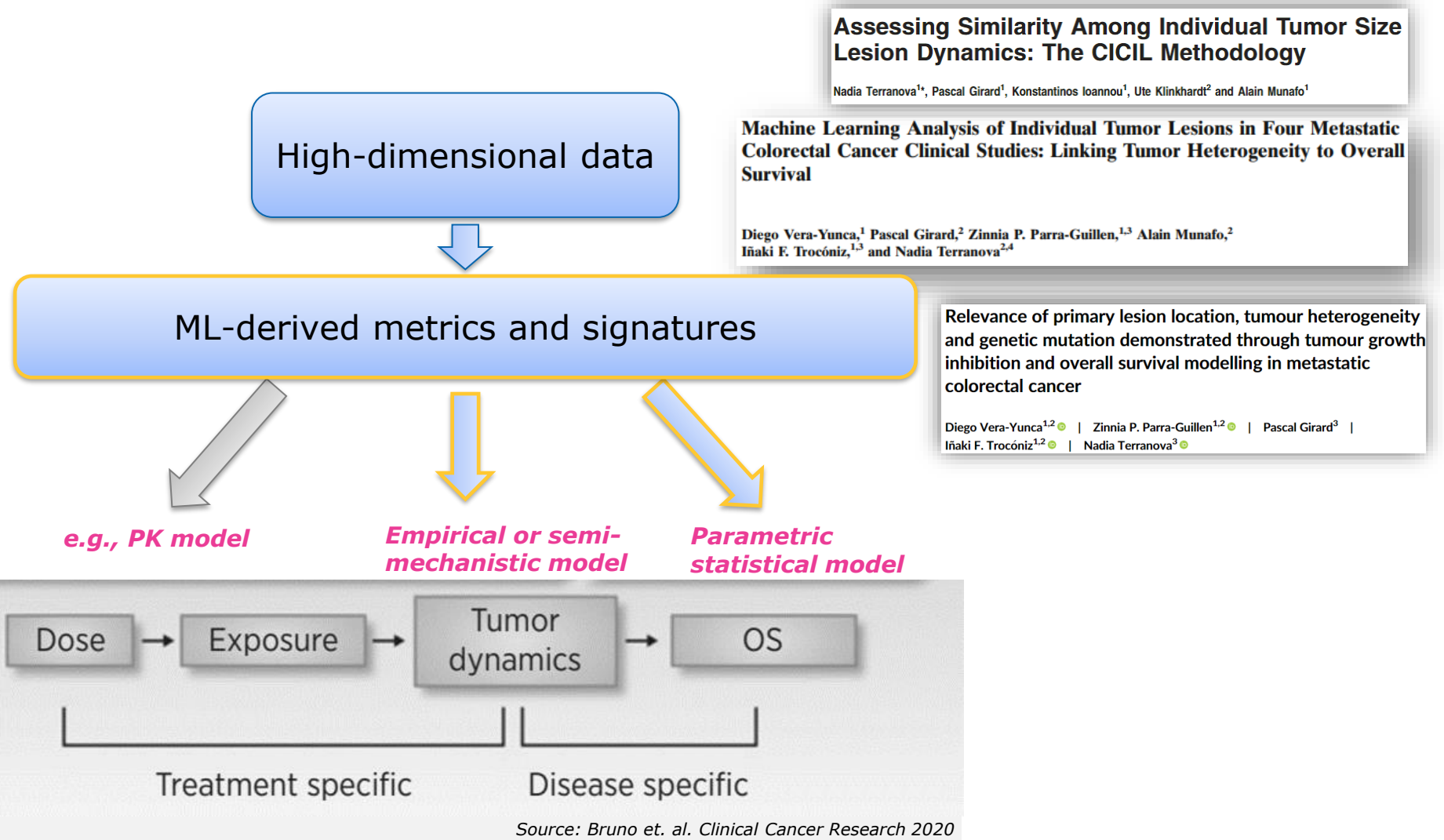
Quantitative radiomics

Integrating radiomics into modeling of real-world tumor dynamics in melanoma patients



ML-derived metrics or signatures related to disease evolution can be identified

Advancing model-informed precision oncology



Assessing Similarity Among Individual Tumor Size Lesion Dynamics: The CICIL Methodology

Nadia Terranova^{1*}, Pascal Girard¹, Konstantinos Ioannou¹, Ute Klinkhardt² and Alain Munafo¹

Machine Learning Analysis of Individual Tumor Lesions in Four Metastatic Colorectal Cancer Clinical Studies: Linking Tumor Heterogeneity to Overall Survival

Diego Vera-Yunca,¹ Pascal Girard,² Zinnia P. Parra-Guillen,^{1,3} Alain Munafo,² Iñaki F. Trocóniz,^{1,3} and Nadia Terranova^{2,4}

Relevance of primary lesion location, tumour heterogeneity and genetic mutation demonstrated through tumour growth inhibition and overall survival modelling in metastatic colorectal cancer

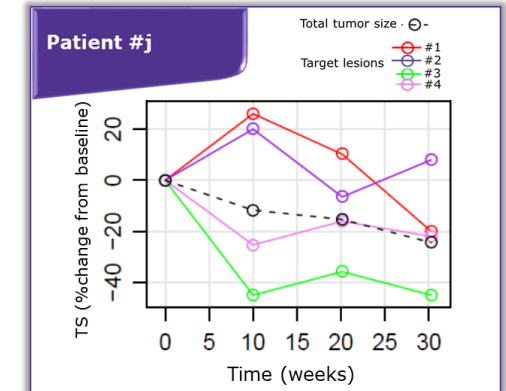
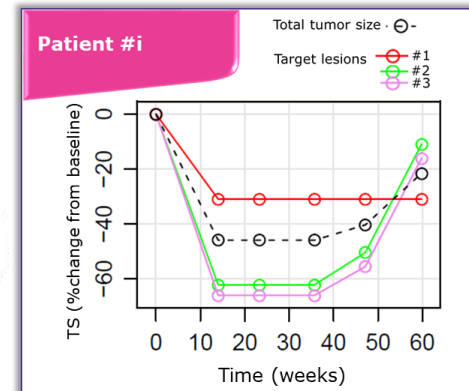
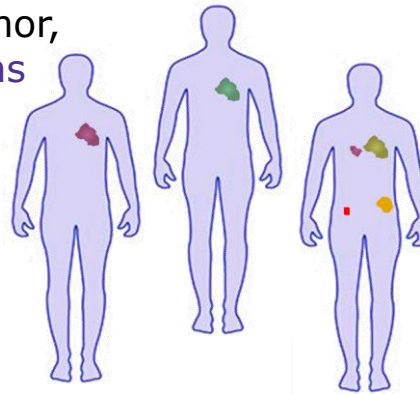
Diego Vera-Yunca^{1,2} | Zinnia P. Parra-Guillen^{1,2} | Pascal Girard³ | Iñaki F. Trocóniz^{1,2} | Nadia Terranova³

Developing a ML-based metric for tumor lesions heterogeneity

Assessing tumor heterogeneity

INTER-TUMOR HETEROGENEITY

Differences exist not only within a single tumor, but also **across patients** and **individual lesions** within the same tissue and patient



How can we assess the **similarity of lesion dynamics in large-scale studies** before modelling?



CICIL: Classification Clustering of Individual Lesions

Classification of individual target lesions
Rule-based classifier

Estimation of the degree of similarity
Cross-correlation

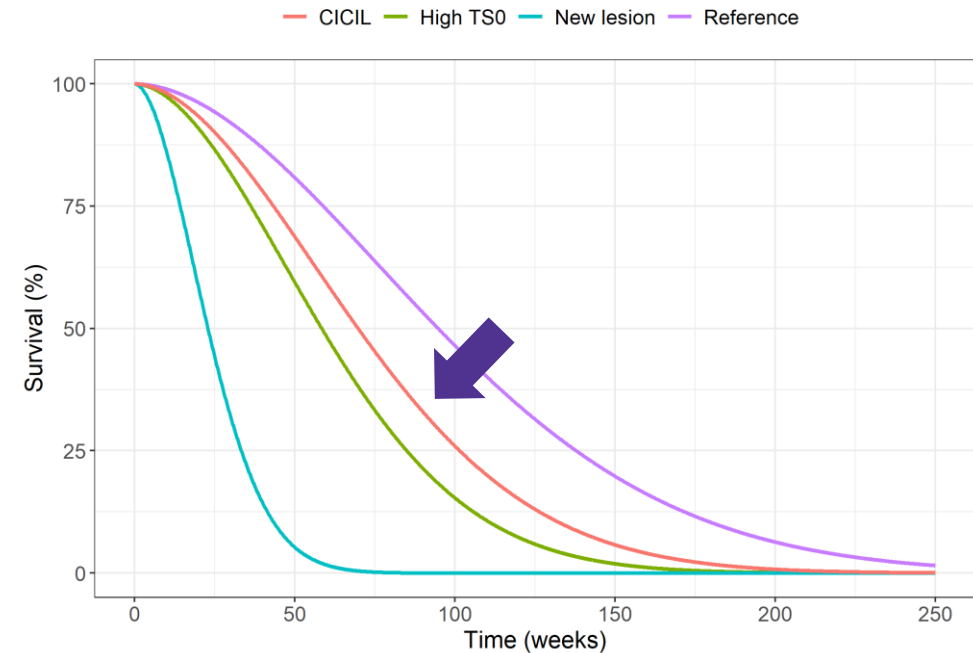
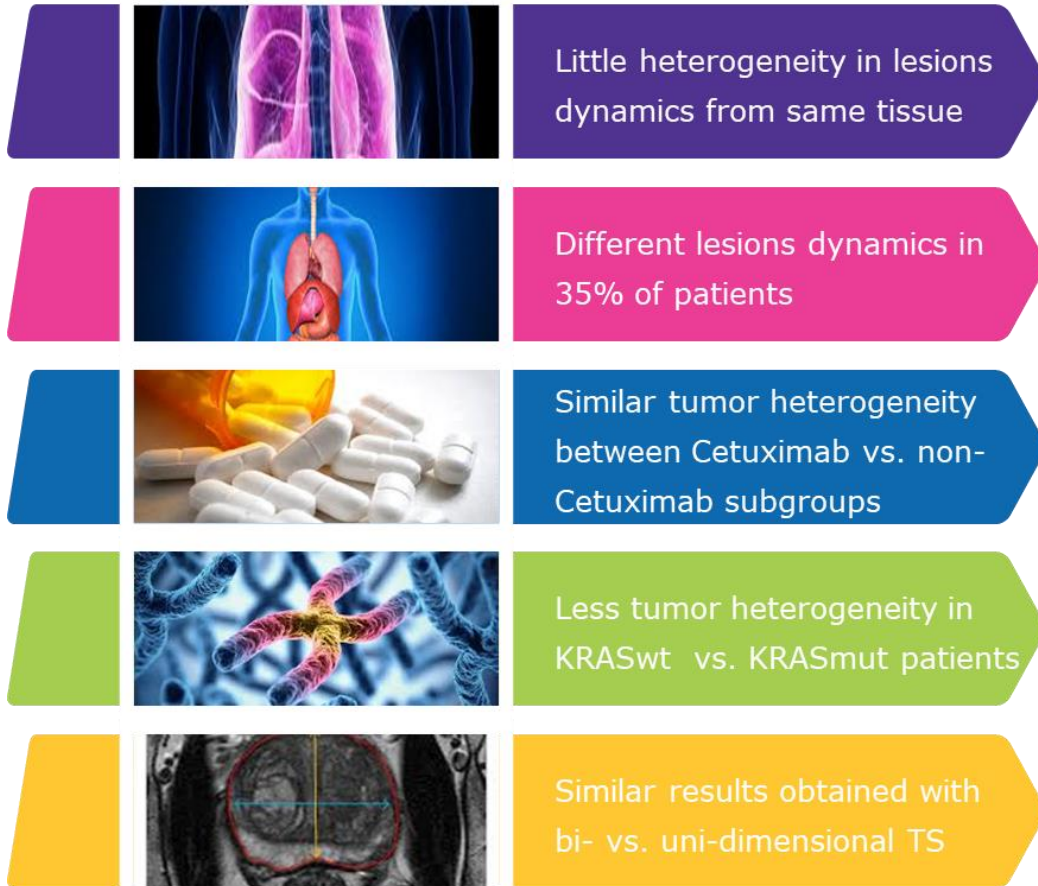
Result exploration and interpretation
K-means clustering

N. Terranova, P. Girard, K. Ioannou, U. Klinkhardt, A. Munafo. Assessing similarity among individual tumor size lesion dynamics: The CICIL methodology. CPT: PSP 2018

Heterogeneity is higher in lesions dynamics across tissues, especially in KRASmut patients, and predictive of OS

Application to cetuximab CRC

The heterogeneity of **6369 individual target lesions** from 1781 mCRC patients was quantified with CICIL



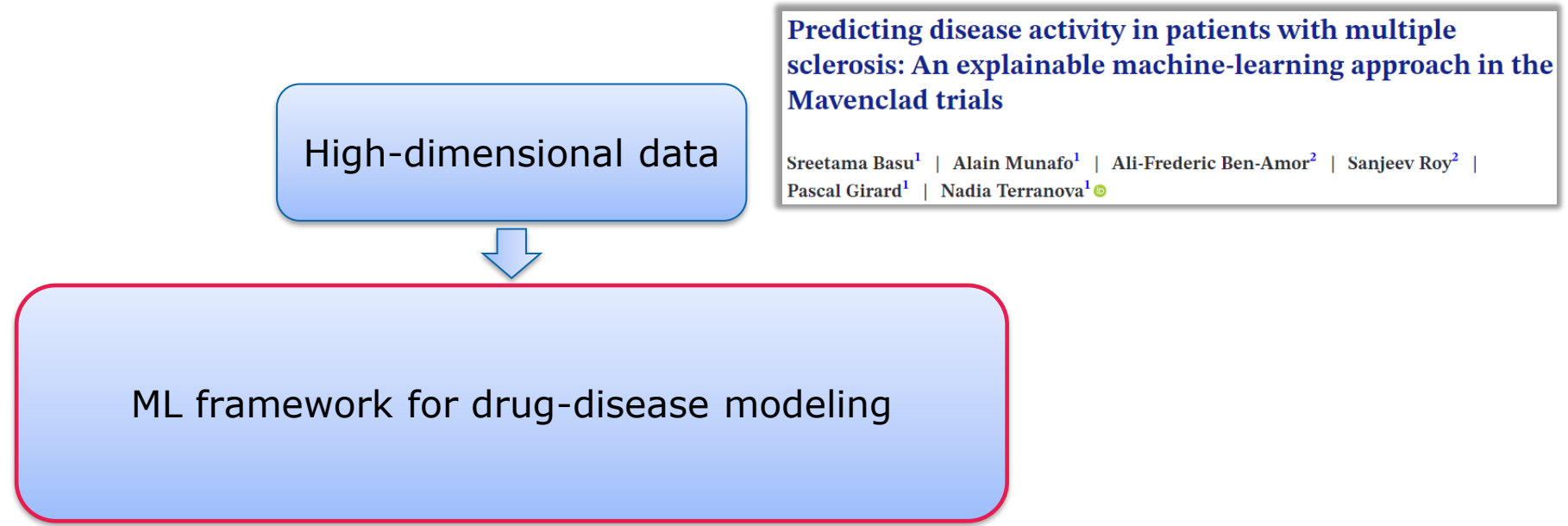
CICIL metric of tumor heterogeneity was a **significant predictor of overall survival**

N. Terranova et al. CPT:PSP 2018
D. Vera-Yunca et al. AAPS J. 2020
D. Vera-Yunca et al. Br J. Clin Pharm 2020

OS: Overall Survival; TS: tumor size; KRASwt: KRAS wild-type; KRASmut: KRAS mutated.
AI/ML-enabled drug-disease modeling | Nadia Terranova | February 17, 2023

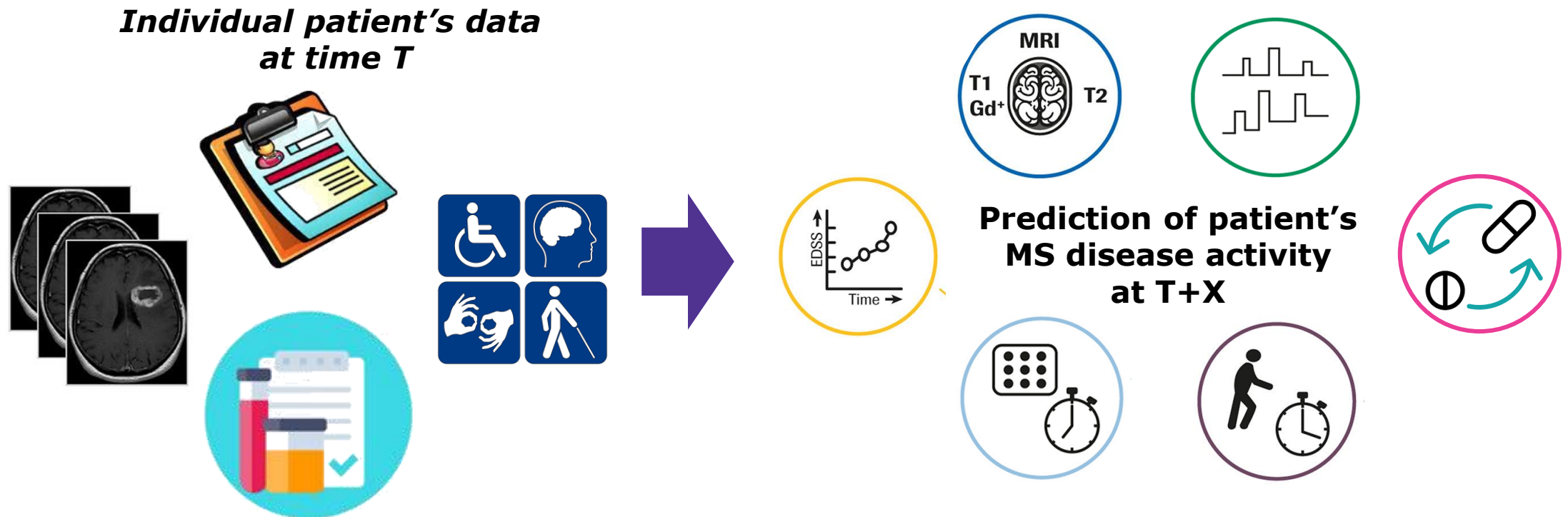
ML enables predictions of clinical endpoints in “mechanism-agnostic” manner

Explainable ML for Disease Progression



Early identification of patients experiencing the onset of MS disease activity in MAVENCLAD trials

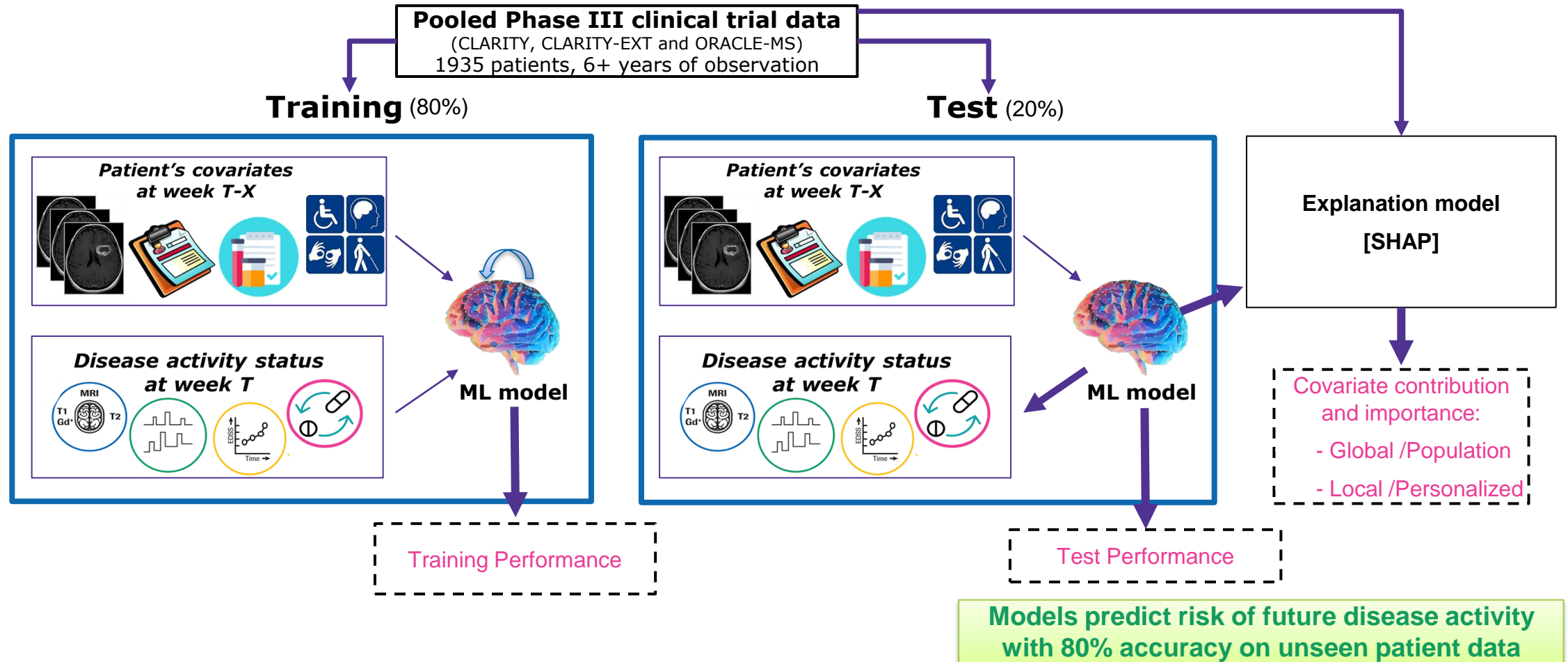
Integrating demographics, response data, MRI and neurological assessments available in cladribine trials to explore which covariates contribute to early identification of MS disease activity by using ML.



Sreetama Basu, Alain Munafo, Ali-Frederic Ben-Amor, Sanjeev Roy, Pascal Girard, Nadia Terranova. "Predicting disease activity in Multiple Sclerosis patients - an explainable Machine Learning approach in Mavenclad trials". CPT:PSP 2022

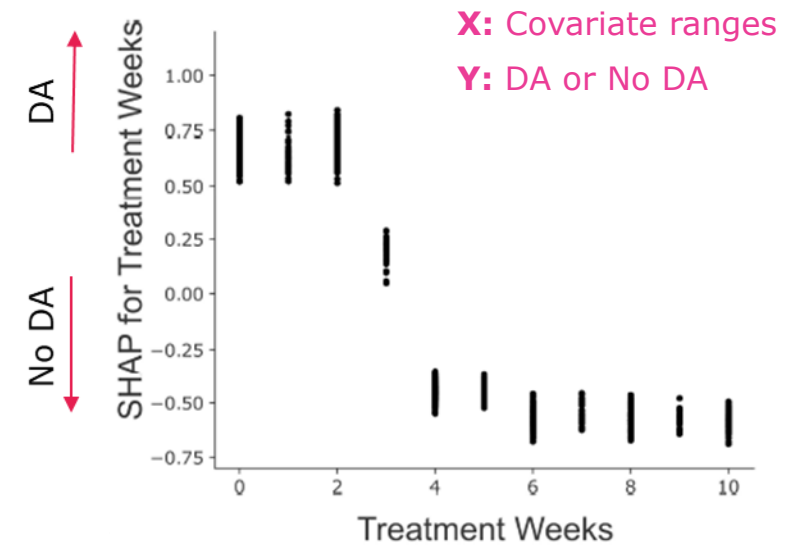
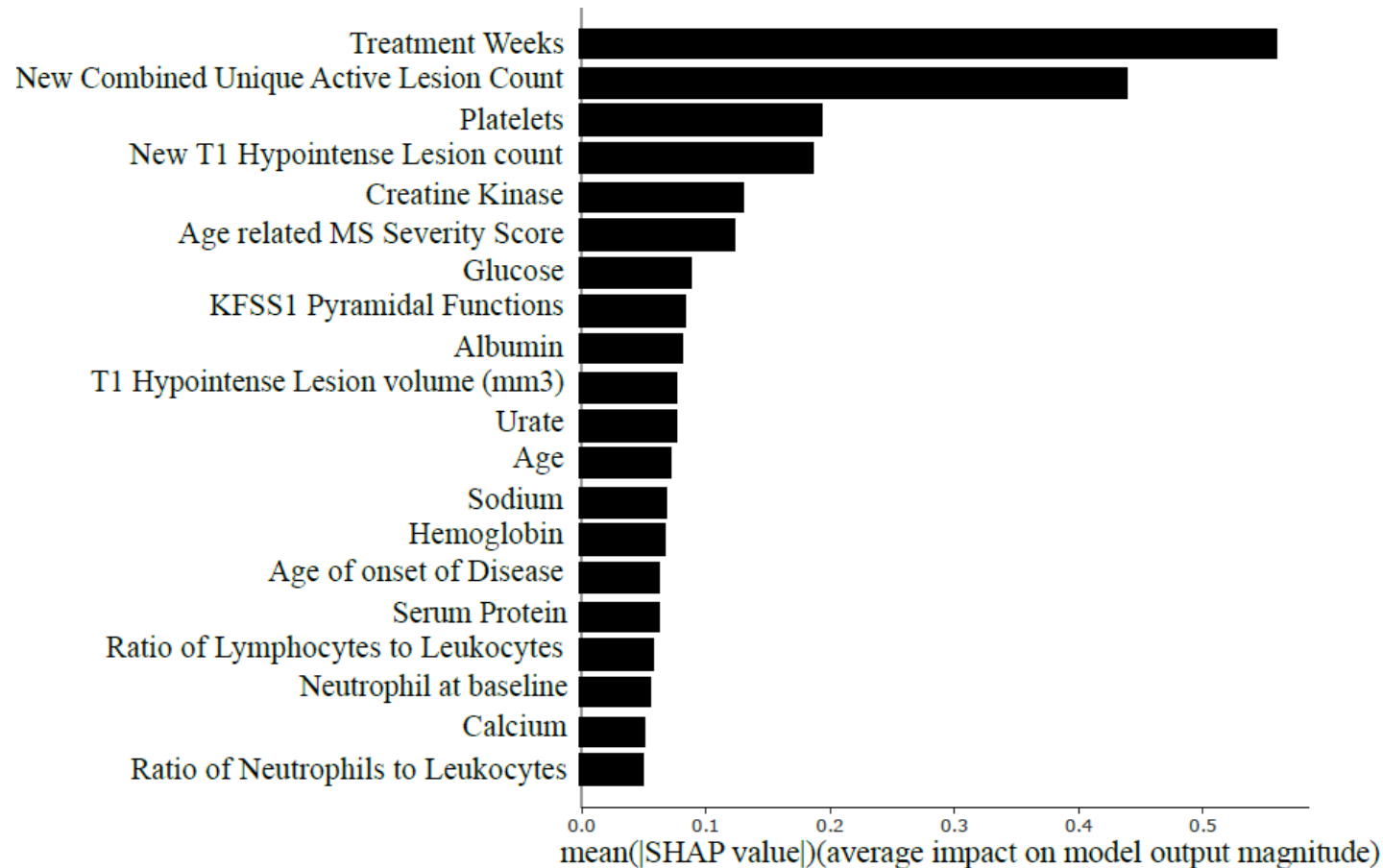
Developed ML models well predict disease activity based on Phase 3-4 covariates

Overview of analysis framework



Treatment weeks, MRI and ARMSS result as top predictors of disease activity

Top predictive covariates

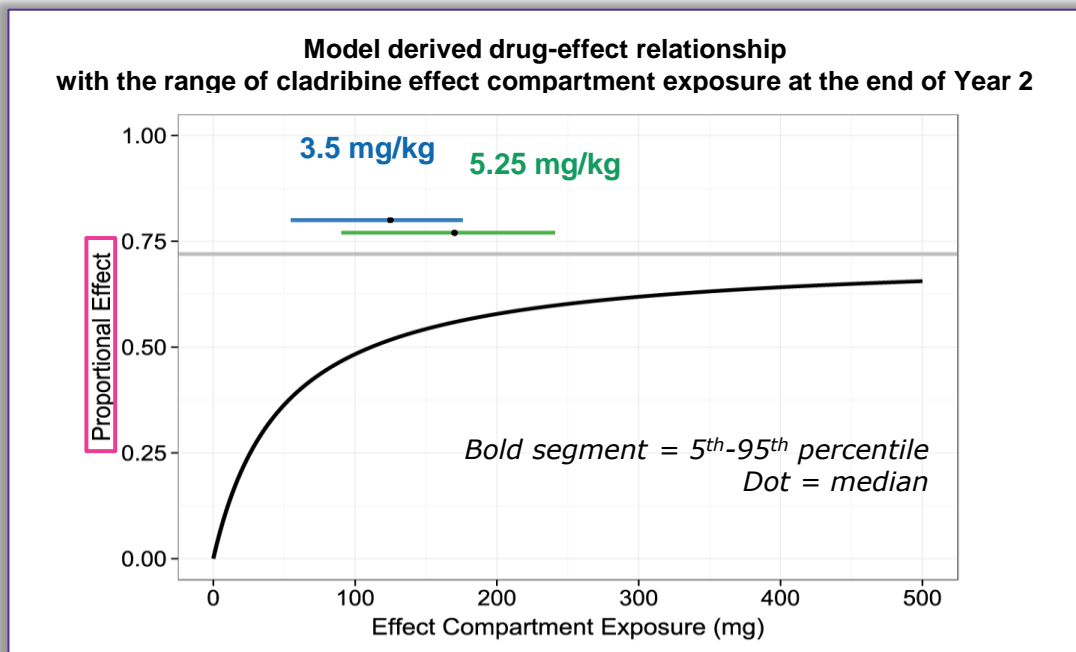


NOTE: Correlations picked by the model do not imply causation

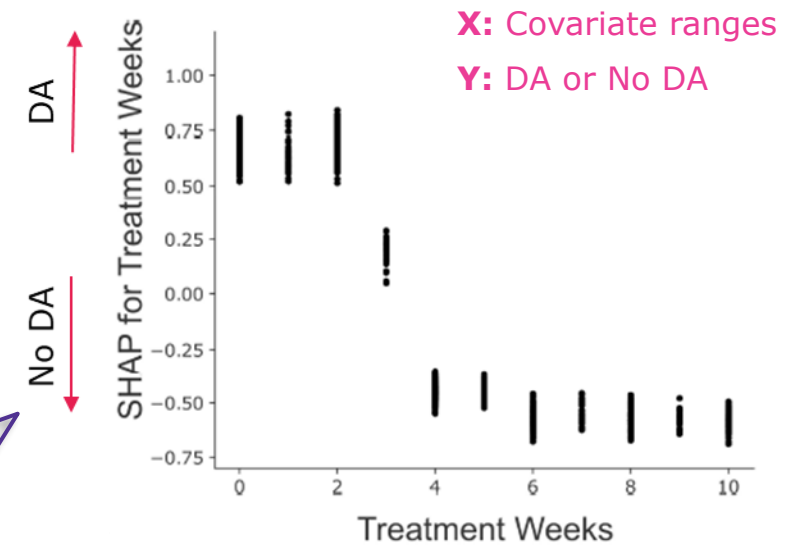
Treatment weeks, MRI and ARMSS result as top predictors of disease activity

Top predictive covariates

Population Repeated Time-to-Event model of qualifying relapses



R. Hermann et al., Clin Pharmacokinet. 2019



DA: Disease Activity; ARMSS: Age-related Multiple Sclerosis Severity Score

To conclude...

Integration of AI/ML in model-informed drug development for precision medicine is increasingly evolving with demonstrated value

- AI/ML allow to mine **heterogenous and high-dimensional dataset** by capturing **nonlinear** effects and variable **interactions**
 - Novel biomarkers (e.g., image-based radiomics, liquid biopsy circulating tumor DNA)
 - Real-World Data (e.g., electronic health records, registries)
 - Digital biomarkers (digital health sensors and devices, reinforcement learning for precision dosing)
 - Translational modeling of safety
- ML can **inform more traditional mechanistic approaches** towards ML-enabled drug-disease modeling.
- Accurate predictions of **patient response time course and clinical outcomes** can be achieved **without prior assumptions** on relationships and underlying mechanisms.
- **Interpretability ML methods** can provide more transparent understanding of the model and results, thus increasing trust.
- Nurturing new **cross-functional collaborations** is key to maximize the value of data

Acknowledgements

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Medical N&I Team

Cladribine Project Team

Cetuximab Project Team

Avelumab Project Team