AI/ML-enabled drug-disease modeling

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

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Quantitative Pharmacology
Advanced Analytics are a strategic Enabler of Translational Precision Medicine

Patient-centered forward and reverse translation

Advanced cloud-based platforms enabling precision medicine hypothesis generation and evaluation with high quality/high volume biomarker analysis and self-service tools for scientists

Reverse-translation of clinical trial -omics data into discovery, improving approaches to patient stratification, trial design, and target selection

Applications of AI/ML for biomarker optimization, digital pathology, and single-cell data analysis

Quantification of the dose-exposure-response relationship, together with factors affecting its variability, to bring best possible therapeutic individualized solutions with the optimal dose, regimen, and prescribing guidance

Integrated ‘system-level’ mechanistic modeling to characterize MoA and pharmacological drug-target interactions in biological systems

Applications of AI/ML into population and translational Systems Pharmacology modeling to accelerate analyses and enable the integration of variety of data amenable to AI/ML

Source: Terranova, N., Venkatakrishnan, K., & Benincosa, L. J. The AAPS Journal, 2021
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
ML-based identification of prognostic and predictive factors of long-term overall survival and tumor growth dynamics

Avelumab JAVELIN Gastric trial

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


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

Advancing model-informed precision oncology

High-dimensional data

ML analysis of prognostic and predictive factors

- e.g., PK model
- Empirical or semi-mechanistic model
- Parametric statistical model

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

Radiomics features
Quantitative description of imaging ROI
>100 features per lesion & timepoint
~230 features per patient

ML-based radiomics feature pre-selection

Example for tumor growth rate constant baseline
1st follow-up - baseline

Abler et al. JCO-CCI In press
Courlet et al. Under review

Covariate assessment with conventional modeling approaches:
radiomics and clinical covariates

Delta Shape Elongation
Baseline image 1st follow-up image
Higher tumor growth rate
ML-derived metrics or signatures related to disease evolution can be identified

Advancing model-informed precision oncology

High-dimensional data

ML-derived metrics and signatures

- e.g., PK model
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Tumor Size-Overall Survival: Current Paradigm

Source: Bruno et. al. Clinical Cancer Research 2020
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

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**

- **Little heterogeneity in lesions dynamics from same tissue**
- **Different lesions dynamics in 35% of patients**
- **Similar tumor heterogeneity between Cetuximab vs. non-Cetuximab subgroups**
- **Less tumor heterogeneity in KRASwt vs. KRASmut patients**
- **Similar results obtained with bi- vs. uni-dimensional TS**

OS: Overall Survival; TS: tumor size; KRASwt: KRAS wild-type; KRASmut: KRAS mutated.

N. Terranova et al. CPT:PSP 2018
D. Vera-Yunca et al. AAPS J. 2020
ML enables predictions of clinical endpoints in “mechanism-agnostic” manner

**Explainable ML for Disease Progression**

Predicting disease activity in patients with multiple sclerosis: An explainable machine-learning approach in the Mavenclad trials

Sreetama Basu | Alain Munafo | Ali-Frederic Ben-Amor | Sanjeev Roy | Pascal Girard | Nadia Terranova

High-dimensional data

ML framework for drug-disease modeling
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.

Individual patient’s data at time T

Prediction of patient’s MS disease activity at T+X


ML: Machine Learning; MS: Multiple Sclerosis
Developed ML models well predict disease activity based on Phase 3-4 covariates.

Overview of analysis framework:

1. **Training** (80%):
   - Pooled Phase III clinical trial data (CLARITY, CLARITY-EXT and ORACLE-MS)
   - 1935 patients, 6+ years of observation

2. **Test** (20%):

3. **Explanation model** [SHAP]:
   - Covariate contribution and importance:
     - Global /Population
     - Local /Personalized

4. **Training Performance**
5. **Test Performance**

Models predict risk of future disease activity with 80% accuracy on unseen patient data.
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

Model derived drug-effect relationship with the range of cladribine effect compartment exposure at the end of Year 2

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

R. Hermann et al., Clin Pharmacokinet. 2019
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
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