ACoP Programming Proposal Example

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- *Session title:*
  Explainable Machine Learning for Disease Progression Modeling & Digital Twins

- *Session description (250 word max):*
  While there is significant interest from both industry & regulatory agencies on applying Machine Learning (ML) to quantitative modeling for drug development applications, several challenges remain: these include the generalizability, interpretability and data requirement of such models. To help address these issues, within the IQ Consortium the AI/ML Working Group was formed with the aim to foster scientific dialogue on ML applications and identify a set of good-practices, so as to enable broader impacts in drug development.

  In view of the significant interest in longitudinal disease progression modeling and the need to disseminate novel ML methodologies that can significantly advance this field, we have put together a session involving experts from the biopharma and AI industries as well as research institution with a focus on key aspects that are crucial towards enabling broader adoption and increased impact within the drug development setting. The talks in the session will present the state-of-the-art developments in applying ML to disease progression modeling. Additionally, the session will cover methodological approaches that can be used to explain model findings and convey the extracted insights to cross-functional stakeholders. Finally, the use of ML in generating Digital Twins with the aim of reducing the size of clinical trials will be demonstrated. The disease areas that will be included will be wide ranging and of broad interest, including oncology, Multiple Sclerosis and Alzheimer's

Disease. With this symposium, we aim to initiate scientific dialogue and collaboration across disciplines to elevate the impact of disease progression modeling with ML.

- *Learning objective (100 word max):*
  The audience will learn about Machine Learning (ML) methodologies for building disease progression models from clinical data and generating the patients' Digital Twins. Additionally, they will hear about how to structure ML models so as incorporate domain knowledge to enable better interpretability, as well as getting a view into the current state-of-the-art explanatory tools that can be applied to explain complex interactions that underlie nonlinear ML models. Applications of the methodologies across several disease areas will be shown and the audience will see how such models could be used to enable the design of smaller clinical trials.

- *Primary Focus:*
  - *Big Data/AI/ML*

- *Proposed Speaker #1:* **Nadia Terranova (Merck Serono)**
  - ***Predicting disease activity in Multiple Sclerosis patients – an explainable ML approach in Mavenclad trials:*** *Multiple sclerosis (MS) is among the most common autoimmune disabling neurological conditions of young adults and affects more than 2.3 million people worldwide. Predicting future disease activity in MS patients based on their pathophysiology and current treatment is pivotal to orientate future treatment. In this respect we used ML to predict disease activity status in MS patients and identify the most predictive covariates of this activity. The analysis is conducted on a pooled population of 1935 patients enrolled in three cladribine Ph3 clinical trials with different outcomes. We applied gradient boosting and SHAP methods to identify patients' covariates that predict disease activity three and six months before their clinical observation, including patient baseline characteristics, longitudinal MRI readouts, neurological and laboratory measures. The most predictive covariates for early identification of disease activity in patients were found to be treatment duration, higher number of new combined unique active lesion count, higher number of new T1 hypointense black holes, and higher age-related MS severity score. This analysis improves our understanding of the mechanism of onset of disease activity in MS patients by allowing early identification in clinical settings and then, enabling better patient monitoring and treatment planning.*

- *Proposed Speaker #2*: **James Lu (Genentech)**
  - ***An Explainable Deep Learning Framework for Tumor Dynamic Modeling and Overall Survival Prediction using Neural-ODE:*** *Tumor dynamic modeling has been widely adopted in supporting the development and approval of oncology drugs. While the existing pharmacometrics models have served well to date,*

with the recent rise of high content datasets the field is facing the challenge of incorporating rich, multi-modal information into existing longitudinal tumor models to provide the actionable insights necessary for personalized therapy. In this work, we propose a foundational deep learning framework, Tumor Dynamic Neural-ODE (TDNODE), based on an encoder-decoder architecture that enables an automated prediction using the observed longitudinal tumor size measurements. By expressing the model in the language of neural networks while being founded upon an abstraction of the process of human modeling, the proposed formalism has the advantage of expressivity, precision and explainability. Using the NSCLC patient data from the clinical trial IMpower150, we show that the model can achieve excellent predictive accuracy at the individual patient level. Furthermore, we demonstrate the ability of encoder outputs from TDNODE to predict patients' Overall Survival and compare the predictive performance to that of the existing tumor growth inhibition (TGI) metrics.

- Proposed Speaker #3: **Stefan Groha (Dana-Farber Cancer Institute)**
    - ***Neural ODEs for Multi-State Modeling and Cause-Specific Time-to-Event Analysis:*** *Survival models are a popular tool for the analysis of time to event data with important applications in medicine. Advances like the Cox proportional hazard model have enabled researchers to better describe hazard rates for the occurrence of single fatal events, but are limited by restrictive modeling assumptions. Moreover, common phenomena are often better described through multiple states, for example, the progress of a disease might be modeled as healthy, sick and dead instead of healthy and dead, where the competing nature of death and disease has to be taken into account. Also, individual characteristics can vary significantly between observational units, like patients, resulting in idiosyncratic hazard rates and different disease trajectories. We propose the use of neural ordinary differential equations as a flexible and general method for estimating multi-state survival models by treating the problem as a dynamic graph. To quantify the uncertainty in the resulting individual cause-specific hazard rates and obtain interpretable results through patient clustering, we further introduce a variational latent variable model. I will introduce both models and show their efficacy in the multi-state setting. After this I will introduce extensions of the model for counterfactual inference and to incorporate domain knowledge.*

- Proposed Speaker #4: **Daniele Bertolini (Unlearn.ai)**
    - **Machine Learning Enables Smaller Clinical Trials:** *Randomized controlled trials are the gold standard to evaluate safety and efficacy of new treatments. Key limiting factors include enrollment difficulties, length, and costs. We developed a novel procedure, Prognostic Covariate Adjustment (PROCOVA™), for which we have received a draft qualification opinion from EMA. PROCOVA™ enables smaller sample sizes, and thus faster and less costly clinical trials, while retaining power and type-I error control. The reduction in sample size is achieved via adjustment for patient-level predictions of the trial outcome. We discuss a case study for Alzheimer's Disease (AD), where we*

developed ML methods that leverage historical data to make predictions to be used with PROCOVA™. We used clinical data from placebo arms of past AD clinical trials and from observational studies to train Conditional Restricted Boltzmann Machines (CRBMs). CRBMs are particularly suited for our applications, as they are generative models and naturally handle multimodality and missing data. Once trained, CRBMs generate clinical predictions with baseline characteristics matched to those of actual clinical trial participants, describing their likely progression under placebo, which we call their Digital Twins. We discuss accuracy of Digital Twins predictions and the implications on sample size reduction of AD clinical trials.