Keynote 1: Model-Informed Drug Development (MIDD) in Alzheimer’s disease: From Data Sharing to Actionable Solutions

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CONFIDENTIAL
Public-Private Partnerships Enable Data Sharing

Creating solutions for drug development through Model-Informed Drug Development (MIDD)

Please email questions to ykarten@c-path.org
Public-Private Partnerships Enable Data Sharing

Creating solutions for drug development through Model-Informed Drug Development (MIDD)
Building quantitative tools for drug development

Fully functioning user tool, e.g. user-friendly simulation app
Building quantitative tools for drug development

Quantitative methods, e.g. models, algorithms

\[ Y_{ij} = f(X_{ij}\beta_i, Z_{ij}\gamma_i, \varepsilon_{ij}) \]

Fully functioning user tool, e.g. user-friendly simulation app
Building quantitative tools for drug development

Standardized, integrated, curated Patient-level data

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Building quantitative tools for drug development

Data Contribution Agreements

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Building quantitative tools for drug development

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Data Contribution Agreements

Foster pre-competitive collaboration

Standardized, integrated, curated Patient-level data

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Execution

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Alzheimer's Disease (AD)

- A mild-to-moderate AD clinical trial simulation tool (built on 3000+ patients, 10 studies) was endorsed by FDA and EMA for optimizing clinical efficacy studies in AD.

- Development of a publicly available user-friendly graphical user interface allows all members of a clinical development team to utilize the tool:

  https://cpath.shinyapps.io/adctsgui/
Alzheimer's Disease (AD)

• A predementia CTS tool was developed (built on 682 patients, 10 studies) and received a letter of support from EMA for optimizing clinical efficacy studies in AD

• The tool utilizes baseline hippocampal volume as a prognostic factor for informing disease progression measured by CDR-SB in additional to other patient features

https://cpath.shinyapps.io/predemctegui/
Beyond AD, several quantitative solutions are being developed to address key drug development needs:

– Trial simulation tools
– Biomarker-based time-to-event analyses
– Outcome measure analyses using Item Response Theory
Parkinson's Disease (PD)

- PD disease progression modeling for submission to FDA and EMA as a clinical trial simulation tool to optimize trial design

- Based on a large aggregated database (built 5000+ subjects, 17 studies) it was possible to quantify disease progress, placebo effects, and medication effects on outcome measures

\[
\begin{align*}
\frac{d\text{Score}_1}{dt} &= r_1 \\
\frac{d\text{Score}_2}{dt} &= r_2 \\
\text{Score}_1 &= \logit^{-1}(\text{Score}_{01} + r_1 \times t) \\
\text{Score}_2 &= \logit^{-1}(\text{Score}_{02} + r_2 \times t) \\
r_1 &= \theta \times \left( \frac{\text{Score}_{01}}{\text{ref(\text{Score}_0)}} \right)^{\beta_{\text{power}}} \\
\frac{d\text{Score}_1}{dt} &= r_1 \times \text{Score}_1 \times \left[ 1 - \frac{\text{Score}_1}{\max(\text{Score}_1)} \right] \\
\frac{d\text{Score}_2}{dt} &= r_2 \times \text{Score}_2 \times \left[ 1 - \left( \frac{\text{Score}_2}{\max(\text{Score}_2)} \right)^{\beta} \right] \\
\frac{d\text{Score}_3}{dt} &= r_3 \times \text{Score}_3 \left[ \ln \left( \frac{\max(\text{Score}_3)}{\text{Score}_3} \right) \right]^\gamma
\end{align*}
\]
Parkinson's Disease (PD)

- Longitudinal Item Response Theory is being applied to MDS-UPDRS part II to quantify the longitudinal dynamics item (5000+ patients with 15000+ item level observations)
- The analysis helps quantify the discriminatory power of the individual items as they compare with each other
- This aims to provide granular understanding of composite measures in PD

\[
P(x > j | \theta, a, b_j) = \frac{1}{1 + e^{-a(\theta - b_j)}}
\]

\[
P_j(\theta) = P(x > j) - P(x > j + 1)
\]
Duchenne Muscular Dystrophy (DMD)

- DMD is a rare genetic based muscular disease occurring in boys, lead to an average life span of 25 years

- Five disease progression models were developed based on stage specific endpoints on the largest analysis dataset in DMD (1100+ subjects, 15 studies)

- Currently submitting to FDA and EMA for regulatory endorsement

\[
\text{Score}_i = G_{\text{max},i} \left(1 - e^{-g_i \times \text{Age}}\right) \times \left(1 - \frac{\text{DP}_{\text{max},i} \times \text{Age}^{\gamma_i}}{\text{DP}_{50,i} + \text{Age}^{\gamma_i}}\right)
\]
Type-1 Diabetes (T1D)

- Presence of Islet Auto Antibodies have been long known to lead to onset of T1D, but no analysis to predict timing to T1D has been done on aggregated patient-level data.

- The T1D consortium and Quantmed have worked to develop a robust time-to-event model that predicts T1D diagnosis timing based on IAAs, patient demographics, and glycemic measures.

- Currently finalizing qualification opinion with EMA.

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In Summary

• Where we have been... **MIDD**

• Where do we want to go... “Quantitatively-Informed Drug Development (QIDD)”

• How...

...by **transforming data into actionable knowledge through collaboration**