INTERNATIONAL CONSORTIUM for INNOVATION & QUALITY in PHARMACEUTICAL DEVELOPMENT

# Opportunities and Challenges of Disease Modeling in Drug Development: IQ Consortium Multi-industry Perspective


***Jin Y. Jin, Ph.D.***

On Behalf of IQ Clinical Pharmacology Leadership Group (CPLG) Disease Progression Modeling (DPM) Working Group:

| | | | |
|---|---|---|---|
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| *Alexander Solms* | Bayer | *Rajendra Singh* | Teva |
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| *Jessica Wojciechowski* | Pfizer | *Yaming Hang* | Takeda |

# Acknowledgement

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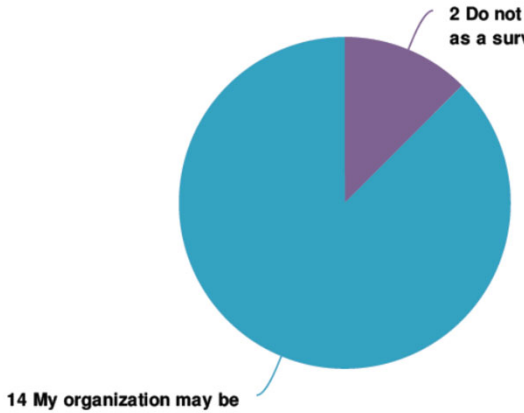
- ***Disease Progression Modeling working group members***
- ***CPLG member companies and their representatives***
- ***IQ office (Lee Nagao, Maja Marshall)***

# Outline

- **Highlights from Cross-industry Survey**
  - Overview
  - Data & Model
  - Application
  - Regulatory Considerations
  - Cross-functional Considerations
  - The Key to Success
- **Case Examples**
  - Neuroscience
  - Immunology
  - Metabolism
  - Oncology
- **Current Status and Call for Action**

***Survey by IQ CPLG DPM working group:***

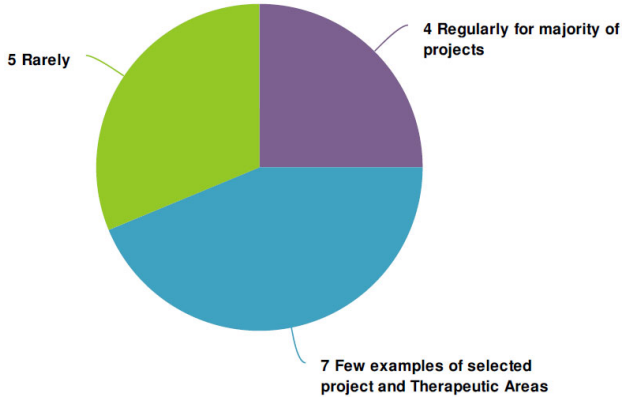
*36 survey questions responded by 16 large-mid size Pharma/Biotech companies (Aug-Sept 2021)*




*AbbVie*
*Biogen*
*Bristol-Myers Squibb*
*Daiichi Sankyo*
*Eisai*
*EMD Serono*
*Genentech*
*GlaxoSmithKline*
*Johnson & Johnson*
*Merck*
*Mitsubishi Tanabe*
*Pfizer*
*Takeda*
*Teva*

# Overview of DPM

**Frequency of DPM:**




**Broad DPM experience across TAs:**

- **Neuroscience (~70%)**
- **Inflammation & Immunology* (>60%)**
- **Oncology – solid (~60%)**
- Metabolic & Endocrine** (>40%)
- Infectious Disease (>40%)
- Oncology – heme (~40%)
- Rare Disease (25%)
- Ophthalmology (n=1)

**"*Disease progression model*" has different representation**

- For **most companies** *disease progression* include:
  - **Natural disease history (>90%)**
  - **Placebo response (>90%)**
  - **SoC as background therapy (>80%)**
- For **some companies** *disease progression* also include:
  - PK/PD or E-R of pharmacodynamic effect time course (50%)
  - QSP (>40%)
  - MBMA, PBPK-PD, TGI modeling (n=1)

**Diverse endpoints** are used to assess disease progression:

- **Clinical endpoints (>90%)**
- **Pharmacodynamic endpoints (>80%)**
- **Biomarkers (75%)**
- Patient reported outcomes (>30%)
- Pharmacogenomics (n=2)

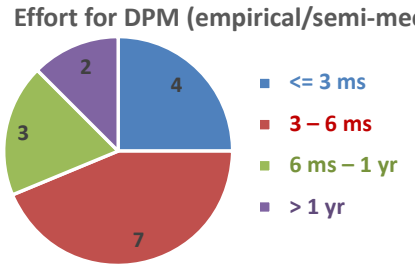
*rheumatology, transplant, pulmonary, allergy, critical care, GI, liver, dermatology, dentistry
**cardiology, nephrology, non-malignant hematology, diabetes, lipid disorders, obesity, general endocrinology, urology, OB/GYN

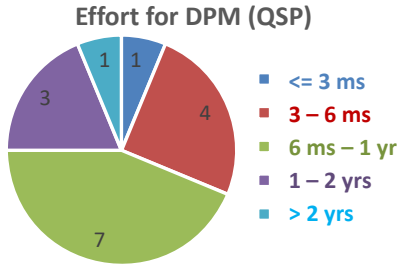
# Data & Model

- **Diverse data source** are used for DPM, including both **individual data** and **aggregated data**:
  - **Internal trial data (all)**
  - **Commercial trial data (>90%)**
  - **Publication (>90%)**
  - **Consortium data (>80%)**
  - **RWE (~70%)**
  - **Observational epidemiological study (>60%)**
  - FDA & regulatory database (>50%)
  - Digital/wearables (>50%)

**Most companies do not have defined workflow/best practice for DPM**

- **Modeling approach** include:
  - **Empirical model (>90%)**
  - **MBMA (>80%)**
  - **Semi-mechanistic model (75%)**
  - QSP (>50%)
  - ML/DL (25%)




- **Time** can be defined in various ways in DPM:
  - **Start of any treatment (75%)**
  - Trial start (>40%)
  - Since diagnosis (>35%)
  - Age (25%)
  - **Time definition varies in DPM depending on the model application scenario (~70%)**
- Multiple approaches for **model evaluation**:
  - Overall diagnostics (all)
  - Sub-group diagnostics including all clinically meaningful covariates (~90%)
  - Simulation based predictive performance evaluation (75%)
  - External validation (~60%)



*DL – deep learning; DPM – disease progression modeling; MBMA – model-based meta-analysis; ML – machine learning; QSP – quantitative system pharmacology*

# Application

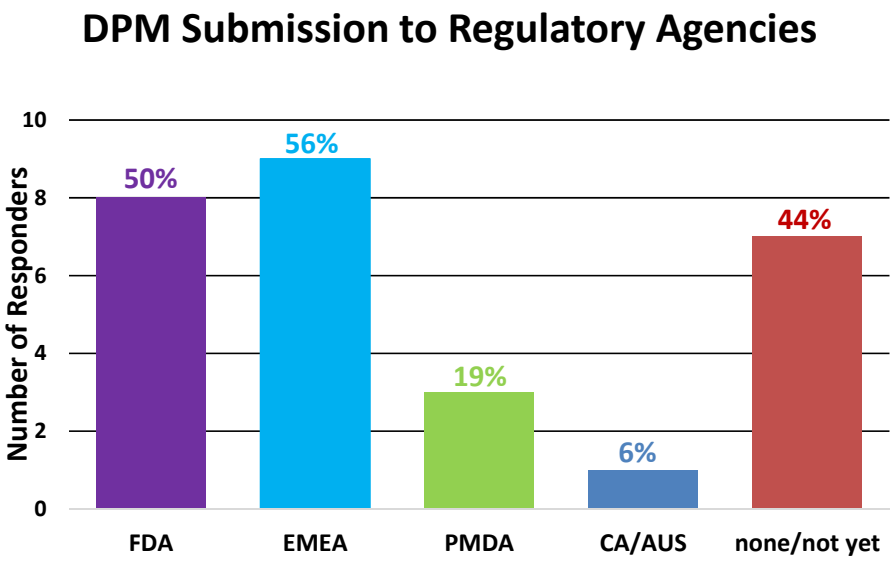
| Development Stage | Application (%) |
|---|---|
| **Pre-IND** | **19 %** |
| **FIH** | **19 %** |
| **Phase Ib** | **50 %** |
| **Phase II** | **88 %** |
| **Phase III** | **63%** |
| **Post-marketing** (PMC/PMR, line extension, new indication, combo, etc.) | **44 %** |

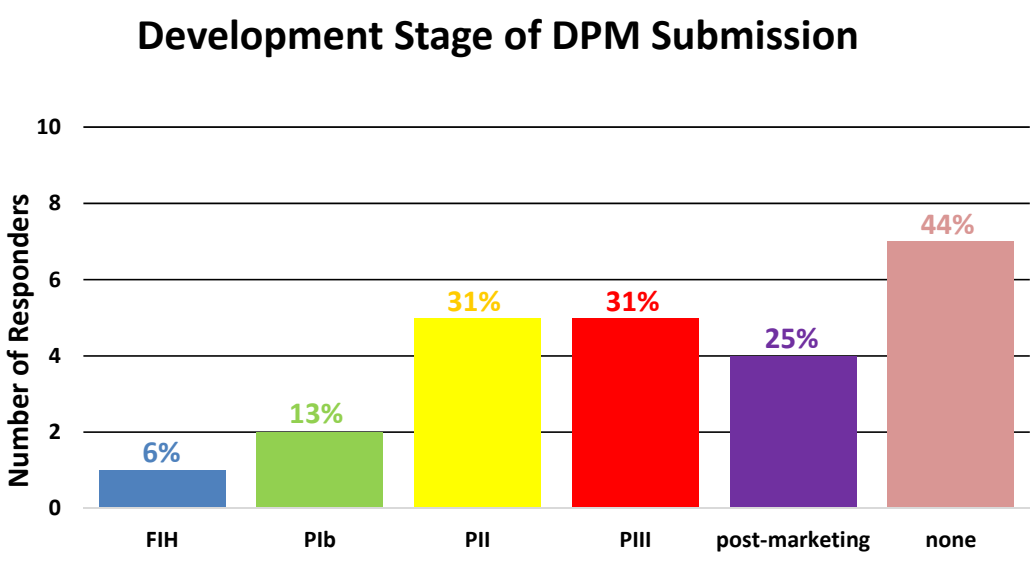
***Demonstrated* Impact of DPM**


- All used DPM for **internal decision making;** only 1 used as part of **major filing**
  - Half of the companies have used DPM for lessons learned from negative trials
- All use DPM to predict outcome in the **same population/indication**
- More than half also use it to predict outcome in **different population/indication with relevant extrapolation**
  - >30% have used DPM developed in adults to extrapolate to **pediatrics**

*DPM – disease progression modeling; FIH – first in human; PMC/PMR – post-marketing commitment/requirement*

# Regulatory Considerations




- **MIDD Pilot Program:** used by 3/16 companies to discuss DPM
- **Milestone regulatory meetings:** 5/16 included questions related to DPM development/application

# Cross-functional Considerations

- **Different disciplines may have their own definition of disease progression**
- **Functions involved in DPM discussion:**
  - **Clinical Pharmacology/Pharmacometrics (all)**
  - **Biostats (75%)**
  - **Clinical (>60%)**
  - Regulatory (25%)
  - Data Management (25%)
  - Preclinical (n=2)
  - Biomarker (n=1)
  - Epidemiology/RWD/HE (n=1)

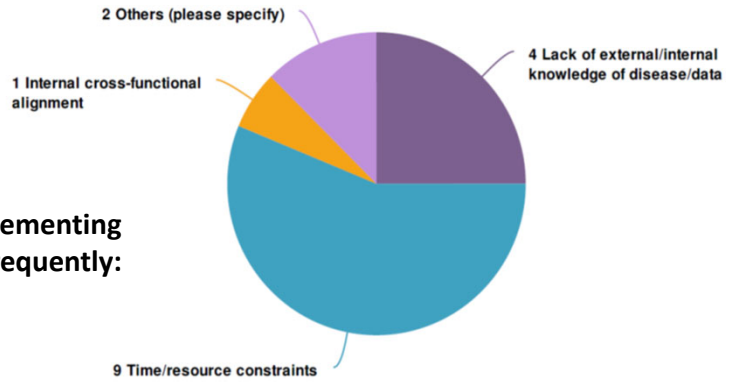
- **Acceptance level of DPM by projects teams/stakeholders:**
  - Widely accepted (n=2)
  - **Accepted by some, but pushbacks by some others (75%)**
  - Very selective acceptance (n=1)
  - Research exploration mainly in Clin Pharm/Pharmacometrics and not yet accepted by others (n=1)



*DPM – disease progression modeling; HE – health economics; RWD – real world data*

# The Key to Success

**The most important reason for not implementing disease progression modeling as frequently:**




| | SUCCESS FACTORS | PAIN POINTS |
|---|---|---|
| **Robust Data and Model:** | | |
| | ❑ **Availability of right data with adequate quality**<br>❑ **Sensitive disease endpoint/surrogate endpoint/biomarker** | ❑ **Inadequate data or data with too large variability**<br>❑ **Lack of good endpoint/biomarker** |
| | ❑ **Fit-for-purpose model selection**: scientific and practical (eg. data, application, timeline)<br>❑ Knowledge of **source of variability** in disease progression | ❑ Lack of good **disease knowledge**<br>❑ Significant **covariates** not included in the model |
| **Impactful Application:** | | |
| | ❑ **Cross-functional team buy-in and alignment**<br>❑ **Sharing example and impact showcase** are **key to foster discussion and acceptance** | ❑ **Lack of impact showcase, especially for regulatory acceptance** |
| | ❑ **Timely delivery** and **effective communication/presentation** to impact development & regulatory decisions | ❑ Data/model not ready in **time** for decision<br>❑ DPM impact also diminished when **decisions were made a priori** |
| **Broad Acceptance:** | | |
| | ❑ **Cross-company consortiums** | ❑ **Non-competitive data and model sharing** |
| | ❑ **Regulatory directions** regarding acceptance and utility of DPM will be significant | ❑ Lack of clear **regulatory guidance and path** |

# 28 Case Examples

| TA | Indication | Data | Model | Drug Development Application | Reference |
|---|---|---|---|---|---|
| Metabolic & Endocrine | OA | PhII | Empirical | Potential: dose selection | (2018) https://www.page-meeting.org/default.asp?abstract=8722# |
| Metabolic & Endocrine | obesity | PhII & III | Empirical | Potential: trial design, trial read-out | (2018) Sharma VD et al. J Clin Pharmacol. 58(2): 240-53 |
| Metabolic & Endocrine | diabetes | ADAG study | Semi-mechanistic | Potential: trial read-out | (2013) Lledo-Garcia R et al. J Pharmacokinet Pharmacodyn. 40(2): 129-42 |
| Metabolic & Endocrine | diabetes | PhI | Semi-mechanistic | Potential: trial design, mechanistic understanding at trial read-out | (2007) Silber HE et al. J Clin Pharmacol. 47(9): 1159-71 |
| Metabolic & Endocrine | diabetes | PhI & II | Semi-mechanistic | Potential: model-based approach for early decision making, trial design | (2013) Kjellsson MC et al. J Clin Pharmacol. 53(6): 589-600 |
| Metabolic & Endocrine | diabetes | PhIII | Semi-mechanistic | Potential: trial design, mechanistic understanding at trial read-out | (2006) de Winter W et al. J Pharmacokinet Pharmacodyn. 33(3): 313-43 |
| Metabolic & Endocrine | diabetes | PhII, literature data | Empirical, MBMA | PhIII dose selection | (2013) Naik H et al. CPT Pharmacometrics Syst Pharmacol. 2(1): e22 |
| Immunology | RA | PhIIb | Empirical | PhII read-out | (2018) https://acrabstracts.org/abstract/exposure-efficacy-analysis-in-dmard-inadequate-response-rheumatoid-arthritis-patients-treated-with-gsk3196165-along-with-methotrexate/ |
| Immunology | RA | PhIIb | Empirical | PhIII dose selection | (2019) M-024 https://isop.memberclicks.net/assets/ACoP10/documents/ACoP10%20Combined%20Abstracts_Monday%2021%20October.pdf |
| Immunology | RA | literature database | MBMA | Dose selection and reduced trial design in new indication | (2021) https://www.page-meeting.org/default.asp?abstract=9811 |
| Immunology | SLE | PhII & III | Empirical | Potential: trial read-out | (2021) ACoP12 |
| Neuroscience | Alzheimer | ADNI consorsium | Empirical | Potential: trial read-out | (2013) Delor I et al. CPT Pharmacometrics Syst Pharmacol. 2(10): 1-10 |
| Neuroscience | Alzheimer | PhIII, literature data | Empirical | PhIII read-out, dosing optimization | (2016) https://www.page-meeting.org/default.asp?abstract=5797 |
| Neuroscience | MS | PhIII | Empirical | treatment guideline (dosing) in clinical practice | (2019) Terranova N et al. Clin Pharmacokinet. 58(3): 325-33 |
| Neuroscience | Parkinson | consortium database | Empirical | Potential: trial design | (2021, *consortium*) Ahamadi M et al. Clin Pharmacol Ther. 110(2): 508-18 |
| Neuroscience | Parkinson | PPMI study | Empirical | Potential: model-based approach for early decision making, trial design | (2021) Sheng Y et al. Br J Clin Pharmacol. 87(9): 3608-18 |
| Oncology | Multiple | preclinical, PhI/Ib/II/III | Empirical | Combo selection, model-based approach for early decision making, trial design, dose selection, regulatory review/decision for dosing label update | (2020, *Review by cross-organization*) Bruno R et al. Clin Cancer Res. 26: 1787-95 |
| Oncology | NSCLC | PhII & III | Empirical | Potential: model-based approach for early decision making | (2018) Claret L et al. Clin Cancer Res. 24: 3292-98 |
| Oncology | CRC | PhI/II/III | Empirical | Potential: model-based approach for early decision making, trial design | (2021) Vera-Yunca D et al. Br J Clin Pharmacol. Epub |
| Oncology | Multiple Myeloma | Flatiron RWD, PhIII from YODA open data access | Empirical | Potential: model-based approach for early decision making, trial design | (2021) https://www.page-meeting.org/default.asp?abstract=9878# |
| Oncology | BC, NSCLC | PhIII | Empirical (multistate) | Potential: model-based approach for early decision making, trial design | (2020) Beyer U et al. Biom J. 62(3): 550-567 |
| Oncology | BC | PhIII | Empirical (multistate) | Potential: model-based approach for early decision making, trial design | (2021) Krishnan SM et al. CPT Pharmacometrics Syst Pharmacol. 10: 1255-66 |
| Oncology | Multiple | PhII & III | ML | Potential: model-based approach for early decision making, trial design | (2021) PT21-007 https://ascpt.onlinelibrary.wiley.com/doi/10.1002/cpt.2167 |
| Oncology | NSCLC | PhII & III | ML | Potential: model-based approach for early decision making, trial design | (2021) Chan P et al. CPT Pharmacometrics Syst Pharmacol. 10: 59-66 |
| Oncology | CRC | PhI/II/III | ML | Potential: model-based approach for early decision making, trial design | (2020) Vera-Yunca D et al. AAPS J. 22(3): 58 |
| Ophthalmology | nAMD | PhII & III | Empirical | PhII read-out, TRT effect assessment | (2019) https://iovs.arvojournals.org/article.aspx?articleid=2746836 |
| Ophthalmology | GA | PhIII | Empirical | Potential: predict DP based on early data, TRT effect assessment at trial read-out | (2019) https://www.page-meeting.org/default.asp?abstract=9184 |
| Ophthalmology | GA | PhIII | ML/DL | Potential: predict DP based on early data, TRT effect assessment at trial read-out | (2021) https://www.page-meeting.org/default.asp?abstract=9624<br>(2021) https://www.page-meeting.org/default.asp?abstract=9683 |



*DL – deep learning; DP – disease progression; MBMA – model-based meta-analysis; ML – machine learning; TRT – treatment*

# Case Examples

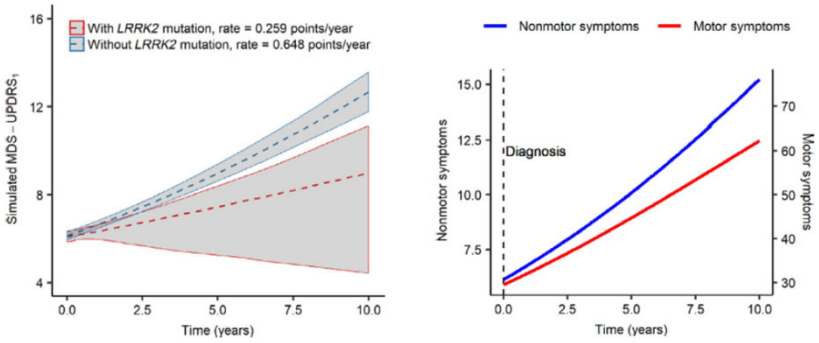
## Neuroscience (Parkinson)

**A Disease Progression Model to Quantify the Nonmotor Symptoms of Parkinson's Disease in Participants With Leucine-Rich Repeat Kinase 2 Mutation**

***Consortium***

Malidi Ahamadi[1,15], Nitin Mehrotra[1], Nathan Hanan[2], Ka Lai Yee[1], Ferdous Gheyas[1], Judith Anton[1], Massimo Bani[3], Babak Boroojerdi[3], Hans Smit[3], Jonas Weidemann[4], Sreeraj Macha[5], Vincent Thuillier[5], Chao Chen[6], Minhua Yang[7], Caroline H. Williams-Gray[8], Glenn T. Stebbins[9], Gennaro Pagano[10], Yaming Hang[11], Kenneth Marek[12], Charles S. Venuto[13], Monica Javidnia[13], David Dexter[14], Anne Pedata[2], Bob Stafford[2], Mussie Akalu[2], Diane Stephenson[2], Klaus Romero[2], Vikram Sinha[1,16,*] and the Critical Path for Parkinson's Consortium

[1]Merck & Co., Inc., Kenilworth, New Jersey, USA; [2]Critical Path Institute, Tucson, Arizona, USA; [3]Union Chimique Belge, Brussels, Belgium; [4]Lundbeck, Copenhagen, Denmark; [5]Sanofi, Chilly-Mazarin, France; [6]GlaxoSmithKline, Brentford, UK; [7]Biogen, Cambridge, Massachusetts, USA; [8]Department of Clinical Neurosciences, University Cambridge, Cambridge, UK; [9]Rush University, Chicago, Illinois, USA; [10]Neuroscience and Rare Disease Discovery and Translational Area, Roche Pharma Research and Early Development, F. Hoffmann-La Roche Ltd, Basel, Switzerland; [11]Takeda, Cambridge, Massachusetts, USA; [12]Institute of Neurodegenerative Diseases, New Haven, Connecticut, USA; [13]University of Rochester, Rochester, New York, USA; [14]Parkinson's UK, London, UK; [15]Current Affiliation: Amgen, Thousand Oaks, California, USA; [16]Current Affiliation: Quantitative Clinical Pharmacology, Millennium Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited, Cambridge, Massachusetts, USA.
*Correspondence: Vikram Sinha (vikram.sinha@takeda.com)

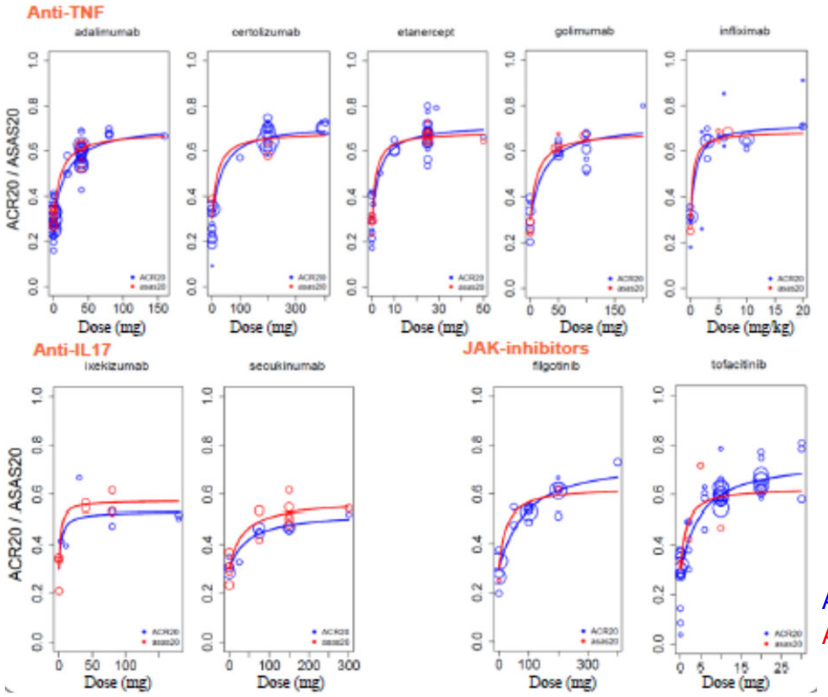



## Immunology (RA, axSpA)

**A Model Based Meta-Analysis for Bridging Treatment Doses of Rheumatoid Arthritis with Axial Spondyloarthritis**

Monica Simeoni[1], Jaap Mandema[2], Stefano Zamuner[1], Anubha Gupta[1]

***MBMA***




ACR20 (RA)
ASAS20 (axSpA)

*axSpA – Axial Spondyloarthritis, MBMA – model-based meta-analysis; RA – Rheumatoid Arthritis*

# Case Examples

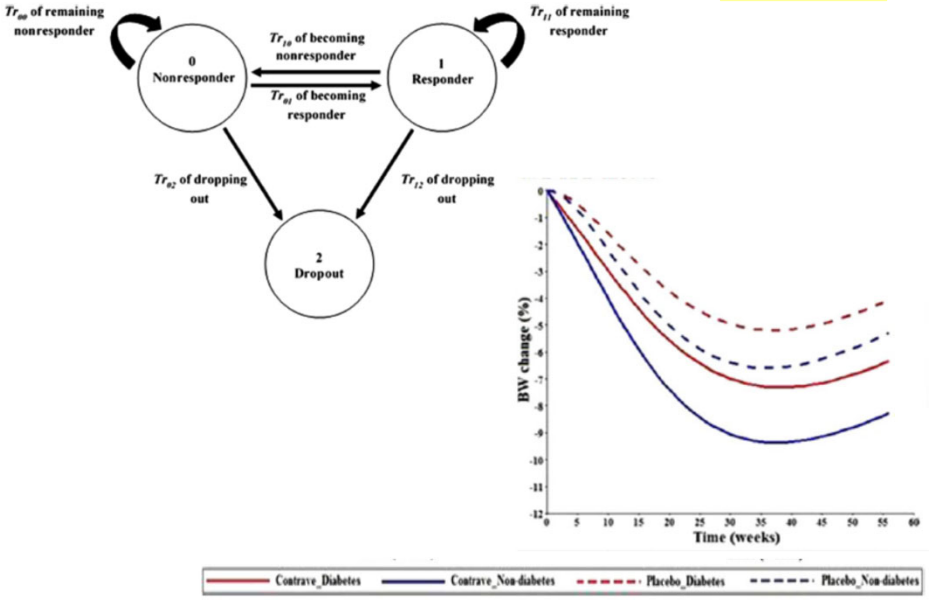
## Metabolic (obesity)

**Model-Based Approach to Predict Adherence to Protocol During Antiobesity Trials**

The Journal of Clinical Pharmacology 2018, 58(2) 240–253
© 2017, The Authors. The Journal of Clinical Pharmacology published by Wiley Periodicals, Inc. on behalf of American College of Clinical Pharmacology
DOI: 10.1002/jcph.994

Vishnu D. Sharma, PhD[1], François P. Combes, PhD[1], Majid Vakilynejad, PhD[2], Gezim Lahu, PhD[3], Lawrence J. Lesko, PhD, FCP[1], and Mirjam N. Trame, PharmD, PhD[1]

***Dropout***




## Metabolic (diabetes)

**A Model-Based Approach to Predict Longitudinal HbA1c, Using Early Phase Glucose Data From Type 2 Diabetes Mellitus Patients After Anti-Diabetic Treatment**

The Journal of Clinical Pharmacology 53(6) 589–600
© The Author(s) 2013
DOI: 10.1002/jcph.86

***Mechanistic***

Maria C. Kjellsson, PhD[1], Valérie F. Cosson, PhD[2], Norman A. Mazer, PhD[2], Nicolas Frey, PharmD[2], and Mats O. Karlsson, PhD[1a]

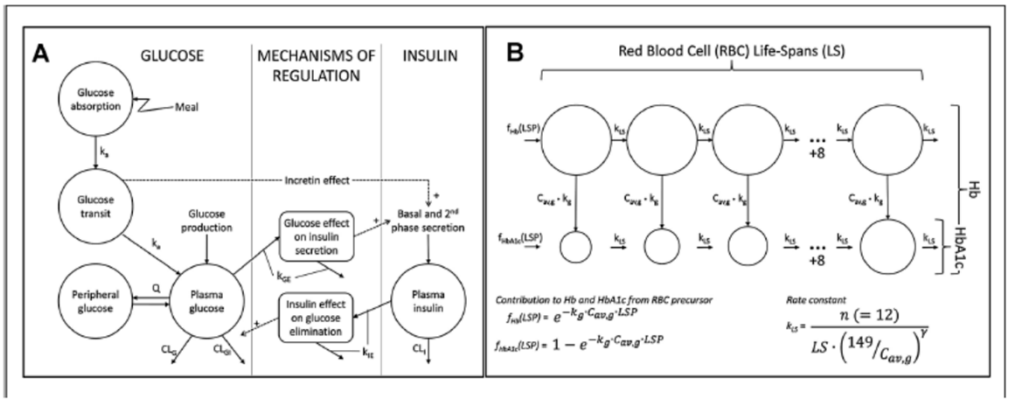



**Figure 1.** Schematic representation of (a) the integrated glucose-insulin (IGI) model adapted from Jauslin et al[6] and (b) the integrated glucose-red blood cells-HbA1c (IGRH) model adapted from Lledo et al.[8] In the IGI model, solid arrows indicate mass flow, while broken arrows indicate mechanisms of regulation. Q, CLG, CLGI, and ka—kinetic parameters of the glucose IGI sub-model; CLI—insulin clearance; kGE and kIE—rate constants for the effect compartments; +, stimulating effect. LSP—life-spans of red blood cell (RBC) precursors; LS—life-spans of RBC; kg—glycation rate constant; $C_{g,av}$—daily average glucose concentration; δ—shape factor for the glucose influence on LS.

# Case Examples

## Oncology

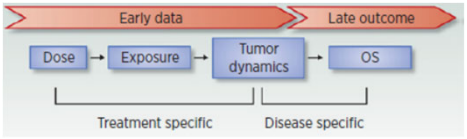
CLINICAL CANCER RESEARCH | REVIEW

**Progress and Opportunities to Advance Clinical Cancer Therapeutics Using Tumor Dynamic Models**

René Bruno[1], Dean Bottino[2], Dinesh P. de Alwis[3], Antonio T. Fojo[4], Jérémie Guedj[5], Chao Liu[6], Kristin R. Swanson[7], Jenny Zheng[8], Yanan Zheng[9], and Jin Y. Jin[10]

[1]Genentech-Roche, Marseille, France. [2]Millennium Pharmaceuticals, a wholly owned subsidiary of Takeda Pharmaceuticals, Inc. Cambridge, Massachusetts. [3]Merck & Co., Inc., Kenilworth, New Jersey. [4]Columbia University, New York, New York. [5]IAME, UMR 1137, INSERM, Université Paris Diderot, Sorbonne Paris Cité, Paris, France. [6]U.S. Food and Drug Administration, Silver Spring, Maryland. [7]Mayo Clinic, Scottsdale, Arizona. [8]Pfizer, Collegeville, Pennsylvania. [9]MedImmune, Mountain View, California. [10]Genentech-Roche, South San Francisco, California.

***Review of Case Studies***



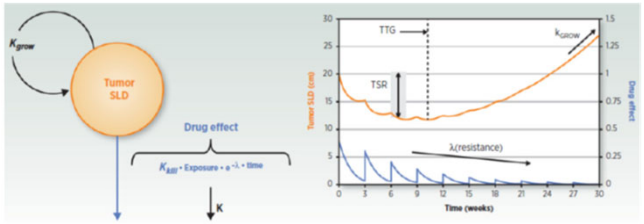




**Table 1.** Summary of case studies with tumor dynamic modeling to inform drug development.

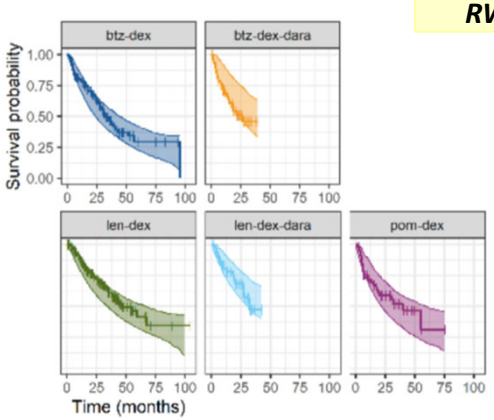
| Question | Data | Process | Findings | Use | References |
|---|---|---|---|---|---|
| Early selection of | PI3Kα/TORC1/2 inhibitors | Response surface of growth | No predicted antitumor effect benefit | R | 53 |

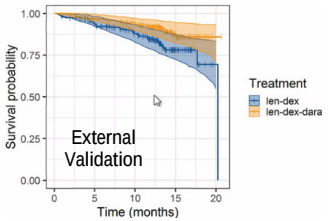
## Oncology (MM)

**A Disease Model for Multiple Myeloma Developed Using Real World Data**

Chanu P, Wang N, Li Z, Chen C, Samineni D, Susilo M, Ogbu U, Williamson M, Marchand M, Li C, Bruno R.

***RWD***



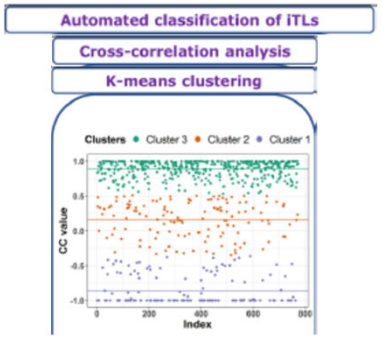



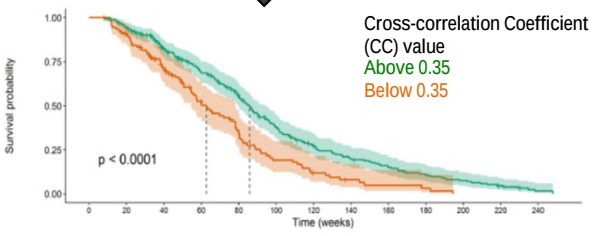

## Oncology (CRC)

**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]

***ML; Individual Tumor Lesion (iTL)***




Cross-correlation Coefficient (CC) value
Above 0.35
Below 0.35



*CRC – colorectal cancer; ML – machine learning; MM – Multiple Myeloma; RWD – real world data*

# Current Status and Call for Action

IQ CPLG DPM Working Group

| | |
|---|---|
| DPM has been **developed** using various data and modeling approaches in many TAs and **applied** at all development stages, but the **science is still evolving** and successful **impact is not certain** | Clear **DPM definition** and aligned **best practice** for convincing cross-functional and regulatory communication |
| Easy access to **relevant and high quality data** for model development/validation is critical and is still limited | Making more disease specific **datasets** and **models** available (especially for **placebo and SoC**) to ensure timely impact |
| Details are lacking in some DPM publications for full **reproducibility**, and publication of successful **impact examples** are currently limited | More **publications** of **reproducible models** as well as **case examples** with demonstrated drug development and/or regulatory decision-making impact are needed |
| **Consortiums** exist for only a few TAs/indications and are generally slow moving | Timely **collaborations**, **consortiums**, **shared learning** are critical, and could be facilitated by regulatory agency |
| Lack of clear **regulatory guidance and path** for DPM, and **regulatory submissions** are limited | More **presentation/publication** and **data/model sharing** **by regulatory agency** on DPM to enhance acceptability and impact for regulatory application and decision-making |

*CPLG – Clinical Pharmacology Leadership Group; DPM – disease progression modeling; SoC – standard of care; TA – therapeutic area*

# Current Status and Call for Action

IQ CPLG DPM Working Group

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