Enablement of hospital-based precision dosing with the DRE

Jeffrey S. Barrett, PhD, FCP, FiSOP

Aridhia Chief Science Officer

Designing the correct dosage regimen is important for achieving the desired therapeutic efficacy and avoiding undesired effects. This is indeed a key component of early-stage drug development. Because of significant homogeneity among humans, the dosage regimen is calculated on a population basis. Late-stage drug development must assess whether there are patient subgroups (e.g., impaired organ function, elderly, pregnancy or pediatrics) that require dose adjustments and of course the sponsor must develop dosage forms that can accommodate the various recommended dosing guidance. Missing a drug dose due to a for any number of reasons could fail the patient's entire treatment regimen. The immediate medical consequences of medication errors might include the formation of blood clots or a failed surgical procedure as examples. In addition, other patient factors not identified during drug development research can later prove to warrant dose adjustment or dose individualization beyond what guidance is included in the initial package insert (drug monograph). Using models to guide dosing in such cases leveraging the available data an augmenting model-based prediction by including available patient-specific data has been an approach used in some, mostly research settings for some time [Jelliffe 1991, Wang 2022].

Precision dosing is an approach to utilize various patient-specific data sources to individualize pharmacotherapy of critical medicines used in the care of disease and other conditions for which drug therapy is recommended. Often the “data” in question refers to therapeutic drug monitoring of drug concentrations in blood or plasma. More recently, biomarkers and clinical outcomes have been utilized to further guide dose individualization for critical pharmacotherapy. The first model-informed precision dosing (MIPD) tool using both PK and PD data was developed in 1969, to ascertain the optimal dosing for patients on anticoagulation therapy [Wang 2022]. The concept has matured over the decades since then with many proposing various methodologies and solutions. Roger Jelliffe, a cardiologist and pharmacometrician was an early pioneer in the field and designed computer software for individualizing drug dosage. He developed optimally precise, individualized drug dosage regimens for patient care involving potentially toxic drugs with narrow therapeutic margins of safety. He was one of the first to integrate physiological parameters into pharmacokinetic data analysis, an approach that today is known as PBPK. He founded the USC Laboratory of Applied Pharmacokinetics in 1973. Much of his early efforts predated the advent of electronic medical records and his early vision involved the training of bedside caregivers with this approach and toolset with chart-based TDM data being hand-entered into a laptop computer with dosing guidance provided immediately at bedside. While his vision was not sustainable for a variety of reasons, it created a concept, a roadmap, and a path forward [Derendorf 2020]. On a personal basis, Roger Jelliffe was a close friend for many years, often visiting me during my tenure at the Children’s Hospital of Philadelphia (CHOP) and the University of Pennsylvania. Dr. Jelliffe gave an excellent Grand Round lecture in 2007 supporting the early days of our Pediatrics Knowledgebase (PKB) efforts at CHOP [Dombrowsky 2011, Barrett 2015] while guiding us with his developing toolset at the Laboratory for Applied PK (LAPK) research [Jelliffe 1991 and Jelliffe 1992].

Over the past several decades, technological advances such as the ubiquity of EHRs, increased data accessibility, and the emergence of cloud-based infrastructure have enabled adoption of MIPD at scale. Still, there is the matter of local champions and governance not to mention advocacy to purchase either entire solutions or the staff and infrastructure to manage locally.

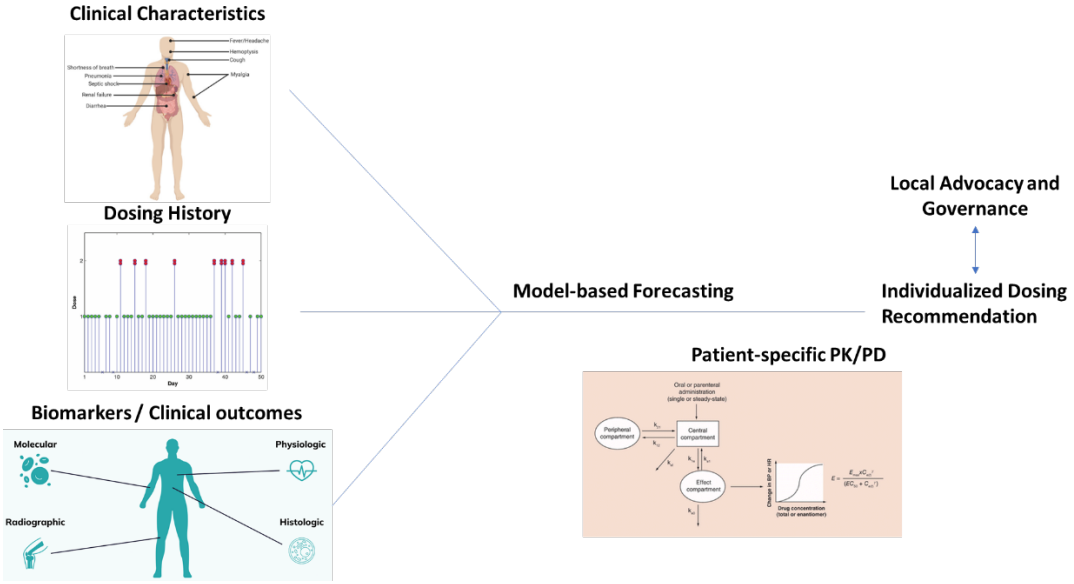

Figure 1. Idealized schematic for the incorporation of essential data towards developing an MIPD strategy and individualized dosing recommendations.

One of the challenges not immediately appreciated by the figure above is the fact that the input data of interest illustrated in the far-left column may not all reside in the same data location and not all are captured in sufficient detail in the electronic medical records. Moreover, different data systems, locations and governance may make the assembly of accurate, real-time data assembly and subsequent analysis particularly challenging.

Aridhia's Digital Research Environment (DRE) provides a secure collaborative research environment for digital analysis of data. Essential companions to the DRE are dynamically updated and searchable metadata catalogs, *in situ* analysis tools with code versioning, as well as data provenance, and audit trails. These features facilitate the collaboration but also make it compatible with regulatory requirements. The Aridhia DRE specifically is the backbone of several highly successful multi-institutional collaborations including the RDCA-DAP and neonatal DAP managed by the Critical Path Institute (CPATH) and the International Neonatal Consortium (INC) respectively [Larkindale 2022, Barrett 2023]. One of the more longstanding implementations of the DRE has been at the Great Ormond Street Hospital (GOSH) in London, UK. Specifically, the DRIVE (Data Research, Innovation and Virtual Environments) initiative from GOSH provides a state-of-the-art unit dedicated to innovation through data and digital technologies, with partnerships across the NHS, industry and academia. While a central component of DRIVE is collaboration an additional effort with the DRE implementation at the hospital and led by several UCL scientists is the use of the DRE coupled with pharmacometric models to explore precision dosing solutions for the patients that walk through the door. A video describing DRIVE and its DRE implementation can be found here, https://www.goshdrive.com/digital-research. Recently, Professor Joseph Standing and myself participated in a webinar exploring the status of precision dosing efforts (both commercial and academic) and discussing the GOSH efforts in the context of functional requirements and necessary

factors which would lead to more collaborative efforts beyond single institution efforts. The You Tube video of the webinar can be found here.

As was discussed in the webinar there are both commercial [Kantasiripitak 2020] and academic [Frymoyer 2020] MIPD solutions. Most precision dosing solutions are reliant on libraries of existing pharmacometric models which have been customized for prospective predictive power when connected to patient level data [Barrett 2021]. Commercial solutions typically come with the promise of validated models and environments which may or may not be connected to the purchasing institutions electronic medical record systems. Some academic and commercial solutions feature web-based solutions where a prescriber is required to enter or upload specific patient records in order to connect to their web environment [Kantasiripitak 2020]. An essential component in either approach is coordination with hospital committees that govern the clinical care processes around pharmacotherapy interventions (e.g., therapeutics standards or drug use evaluation committees). Likewise, considerations for compliance with regulatory standards must also be made.

In the United States the Food and Drug Administration (FDA) performs rigorous statistical and pharmacometric quantitative analyses to replicate the sponsor's analyses, and to understand better which patients will most likely receive benefit from a new drug. Patient factors that may be considered include sex, body size, organ function, age, genotype, concomitant medications, and disease severity. The FDA may choose to change labeled doses for certain subgroups (e.g., gender, renal function, age), based on either the sponsor's or their own PK/PD analyses, when the supportive data are available. However, few options are available if the sponsor chooses not to integrate biomarker data into the design of the phase III trial. Furthermore, the dosage regimen in the approved label will either indicate quantitative or qualitative (e.g., increase/decrease) dose adjustments based on patient factors known to alter the PK and/or PD of the drug. However, it is relatively rare that dosage regimens will be recommended for patients who present with multiple characteristics known to alter drug disposition or efficacy (e.g., decreased renal function plus a drug interaction plus a polymorphic genotype).

In 2019, FDA invited hospital representatives, software developers, and practicing precision-dosing physicians to a working session on how to best promote the widespread adoption of precision dosing. They discussed a variety of challenges to implementing an evidence-based dosing regimen in hospital or clinic setting, from current drug labeling practices to incomplete clinical trial populations, insufficient predictive models for major drug clearance mechanisms, and an overall lack of real-world data. Hopefully, this will not be the last meeting of this stakeholder group. It will be important for future meetings to include a global perspective as healthcare systems, prescribing practices and event the standard of care vary widely on a global scale.

A tremendous opportunity exists with the enablement of precision dosing strategies within the capabilities of a digital research environment (DRE). The two distinct advantages I see are flexibility and collaboration driven. It is a benefit to patients in general to have dosing guidance informed by diverse patient populations (certainly beyond the boundaries of a single institution). This goes beyond the drug model as the standards of care are different around the world as well as the global marketplace for available treatments. Why not benefit from this collective knowledge? Also, for

LMICs and geographic regions with limited infrastructure, sharing and collaborative environments is a means to normalize the knowledgebase and experience.

Precision Medicine challenges principles of equal access to health care services even in a public-based health care system. Recently, Green et al [Green 2023] have reviewed PM-initiatives in the United States, Austria, and Denmark. The authors suggest that PM hinges on—and simultaneously affects—access to healthcare services, public trust in data handling, and prioritization of healthcare resources. Solving the diversity and disparities of global healthcare is beyond the scope of the PM initiative but recognizing that this is the landscape that we all must work with also suggests that flexible solutions are more likely to promote collaboration and actual data and knowledge sharing recognizing that security and patient privacy cannot be sacrificed.

Tags: Aridhia, DRE, MPRINT, Precision medicine, precision dosing, MIPD, Sander Vinks, Mike Neely, GOSH, DRIVE, Joe Standing, Sebastian Wicha, Cincinnati Children's Hospital, Radboud Hospital, Children's Hospital of Philadelphia

References:

Wang Y and Goswami S. Understanding FDA's Perspective on Precision Dosing. Applied Clinical Trials 2022. https://www.appliedclinicaltrialsonline.com/view/understanding-fda-s-perspective-on-precision-dosing

Derendorf, H., Peloquin, C. Roger W. Jelliffe, M.D. (1929–2020). Clin Pharmacokinet 59, 1063 (2020). https://doi.org/10.1007/s40262-020-00928-5

Dombrowsky E, Jayaraman B, Narayan M, Barrett JS. Evaluating Performance of a Decision Support System to Improve Methotrexate Pharmacotherapy in Children with Cancer. J. Ther. Drug Monitoring 33(1): 99-107, 2011.

Barrett JS. Pediatric models in motion: Requirements for model-based decision support at the bedside. British J Clin Pharmacol 79(1):85-96, 2015.

Jelliffe RW, Iglesias T, Hurst A, Foo K, and Rodriguez J: Individualizing drug dosage regimens: comparison of two types or pharmacokinetic models of gentamicin, three methods of fitting serum level data, and several monitoring strategies; Clinical Pharmacokinetics, 21(6):461-478,1991.

Jelliffe RW, Schumitzky A, Van Guilder M: A simulation study of factors affecting aminoglycoside therapeutic precision. Drug Invest. 4 (1):20-29,1992.

Larkindale J, Betourne A, Borens A, Boulanger V, Theurer Crider V, Gavin P, Burton J, Liwski R, Romero K, Walls R, Barrett JS. Innovations in Therapy Development for Rare Diseases Through the Rare Disease Cures Accelerator-Data and Analytics Platform. Ther Innov Regul Sci. 2022 Jun 6. doi: 10.1007/s43441-022-00408-x. Epub ahead of print. PMID: 35668316.

Barrett JS., Betourne A, Walls R, Borens A, Roddy W, Lasater K, Russell S. The future of Rare Disease Drug development: the Rare Disease Cures Accelerator Data Analytics Platform. J Pharmacokinet Pharmacodyn. 2023 May 2. doi: 10.1007/s10928-023-09859-7. PMID: 37131052.

Frymoyer A, Schwenk HT, Zorn Y, Bio L, Moss JD, Chasmawala B, Faulkenberry J, Goswami S, Keizer RJ, Ghaskari S. Model-Informed Precision Dosing of Vancomycin in Hospitalized Children: Implementation and Adoption at an Academic Children's Hospital. Front Pharmacol. 2020 Apr 29;11:551. doi: 10.3389/fphar.2020.00551. PMID: 32411000; PMCID: PMC7201037.

Barrett JS, Barrett RF, Vinks AA. Precision Dosing in Children. J Clin Pharmacol. 2021, 61(S1): S36–S51.

Kantasiripitak W, Van Daele R, Gijsen M, Ferrante M, Spriet I, Dreesen E. Software Tools for Model-Informed Precision Dosing: How Well Do They Satisfy the Needs? Front Pharmacol. 2020 May 7;11:620. doi: 10.3389/fphar.2020.00620. PMID: 32457619; PMCID: PMC7224248.

Green, S., Prainsack, B. & Sabatello, M. Precision medicine and the problem of structural injustice. Med Health Care and Philos 26, 433–450 (2023). https://doi.org/10.1007/s11019-023-10158-8