**MODEL-INFORMED PRECISION DOSING: BACKGROUND, REQUIREMENTS,
VALIDATION, IMPLEMENTATION AND FORWARD TRAJECTORY OF
INDIVIDUALIZING DRUG THERAPY**

Adam S. Darwich¹, Thomas M. Polasek^{2,3,4}, Jeffrey K. Aronson⁵, Kayode Ogungbenro⁶,
Daniel F. B. Wright⁷, Brahim Achour⁶, Jean-Luc Reny^{8,9}, Youssef Daali⁸, Birgit Eiermann⁹,
Jack Cook¹⁰, Lawrence Lesko¹¹, Andrew McLachlan¹², Amin Rostami-Hodjegan^{4,6,*}

¹ *Logistics and Informatics in Health Care, School of Engineering Sciences in Chemistry,
Biotechnology and Health (CBH), KTH Royal Institute of Technology, Stockholm, Swede*

² *Department of Clinical Pharmacology, Royal Adelaide Hospital, Adelaide, Australia*

³ *Centre for Medicines Use and Safety, Monash University, Melbourne, Australia*

⁴ *Certara, Princeton, New Jersey, USA*

⁵ *Centre for Evidence Based Medicine, Nuffield Department of Primary Care Health
Sciences, Radcliffe Observatory Quarter, UK*

⁶ *Centre for Applied Pharmacokinetic Research, The University of Manchester, UK*

⁷ *School of Pharmacy, University of Otago, Dunedin, New Zealand*

⁸ *Geneva Platelet Group, Faculty of Medicine, University of Geneva, Geneva, Switzerland*

⁹ *Inera AB, Swedish Association of Local Authorities and Regions, Stockholm, Sweden*

¹⁰ *Drug Safety Research & Development, Pfizer Inc., Groton, USA*

¹¹ *Center for Pharmacometrics and Systems Pharmacology, University of Florida, Orlando,
USA*

¹² *School of Pharmacy, The University of Sydney Faculty of Medicine and Health, Sydney,
Australia*

**Communicating Author: Prof. Amin Rostami-Hodjegan,
Address: CAPKR, University of Manchester, Stopford Building, Oxford Road, Manchester,
M13 9PT, UK; Tel: +44 161 3060634
Email: amin.rostami@manchester.ac.uk*

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AIMING FOR MODEL-INFORMED PRECISION DOSING

ABSTRACT

Model-informed precision dosing (MIPD) has become synonymous with modern approaches for individualizing drug therapy, considering characteristics of each patient as opposed to a “one-size-fits-all” alternative. This review provides a brief account of the current knowledge, practices and opinions on MIPD whilst defining an achievable vision for MIPD in clinical care based on available evidence. A number of themes are covered from respective domain experts, starting with a historical perspective on variability in dose requirements, before addressing technical aspects of MIPD, including the need for clinical decision support tools, practical validation, and implementation of MIPD in healthcare. Novel ways to characterize patient variability, beyond common perceptions of genetic control, are also discussed. Finally, this review addresses current debates on MIPD from the perspectives of the pharmaceutical industry, healthcare economics and drug regulators.

KEYWORDS

Model-informed precision dosing (MIPD), individualized dosing, pharmacokinetic/pharmacodynamic modelling, systems pharmacology, clinical decision support systems, electronic health records.

INTRODUCTION

Prescribing medicines is one of the most challenging responsibilities in healthcare. The principles are simple: “Choose the appropriate dosage regimen for the right drug, at the right time, and then monitor the outcomes”. In practice, it is much harder. An increase in the number and effectiveness of drug therapies has led to positive gains in life expectancy. However, this means that patients are generally older, suffer from multiple comorbidities, and are medically more complex than a generation ago. Failed drug therapies are therefore common, albeit difficult to quantify, and adverse drug reactions (ADRs) continue to cause significant patient harm and financial burden.(1) Smarter ways to use limited healthcare resources are needed to create long-term sustainable systems that improve patient outcomes. Greater attention to selecting the right dose for a patient, rather than just the default registered dose, is therefore a public health priority.(2; 3) This is commonly called “precision dosing”, also known as personalized or individualized dosing.(4; 5)

The idea that modelling and simulation (M&S) could inform precision dosing dates back to the late 1960s with the work of Dr Lewis B. Sheiner and Dr Roger W. Jelliffe.(6; 7) There is currently a resurgence in the field and a new acronym, MIPD (model-informed precision dosing), (8) which may be defined as prediction of a drug dosage regimen that is most likely to yield a better benefit-to-harm balance than traditional dosing for a given patient, based on their individual characteristics, using computer modelling and simulation.(9) A groundswell of enthusiasm for MIPD occurred in the years following President Obama’s State of the Union Address on precision medicine in January 2015.(10) A healthcare summit on MIPD was held in Manchester in May 2016,(11) an Asian symposium on precision dosing was presented in Busan in December 2018,(12) and the US Food and Drug Administration (FDA)

convened a public workshop on the topic in Bethesda in August 2019¹. Some landmark advances for MIPD have been published recently, including the virtual twin concept to predict pharmacokinetics,(13) liquid biopsy technologies to quantify hepatic drug metabolizing enzyme activities in vivo(14) and account for inter-individual variations in measurements which are not related to abundance of enzymes and transporters,(15) quantitative system pharmacology and toxicology models to better describe pharmacodynamics,(16) and randomized controlled trials showing superior clinical outcomes with MIPD compared to traditional dosing.(17)

The aim of this review is to advance the debate and discussion on MIPD further by defining an achievable vision for MIPD in clinical care. The paper covers a number of themes from respective domain experts, starting with a historical perspective on variability in dose requirements, before addressing technical aspects of MIPD, including the clinical need for dosing decision support tools, practical validation and implementation of MIPD in healthcare, and novel ways to characterize patient variability for M&S. The final parts of the review discuss the latest on MIPD from the perspectives of the pharmaceutical industry, healthcare economics and drug regulators.

A PHYSICIAN'S PERSPECTIVE ON VARIABILITY IN DOSAGE REQUIREMENTS: SOURCES OF VARIABILITY, TERMINOLOGY, AND STRATEGIES

Although doctors have known about variability in human responses to pharmacological interventions since doctoring began, only in the 1970s did the *sources* of such variability start

¹ <https://www.fda.gov/drugs/precision-dosing-defining-need-and-approaches-deliver-individualized-drug-dosing-real-world-setting>

to be elucidated.(18; 19) Variability in drug response can origin from different sources, some of which relate to genetics:

- *Pharmaceutical variability* reflects differences in pharmaceutical formulations, drug amount, rate of release, or both. This variability is non-genetic.
- *Pharmacokinetic variability* arises from differences in the rate and extent of drug absorption, distribution, and clearance. Many patient attributes determining drug absorption (bile release, gastrointestinal motility etc.) and the conditions upon drug administration (concomitant drugs/food), have non-genetic origins. The disposition is determined by a mixture of genetic (e.g., drug metabolism and transport) and non-genetic (e.g., renal function) factors.
- *Pharmacodynamic variability* arises from differences in the responses at the site of action, whether targets for beneficial or harmful effects and is largely genetic in origin.

Genetic factors that determine variability in dosage requirements may result from single gene polymorphisms but are more often polygenic. Non-genetic factors may be endogenous (physiological or pathological) or exogenous (diet or other medicines). Few pharmacological outcomes can be fully explained by a single genetic test.

Terminology

Since the 1970s clinicians have sought ways of devising individual dosage regimens to achieve a favorable benefit-to-harm balance. Different terms have arisen: “individualized”, “personalized”, “stratified”, and “precision”, variously coupled with terms such as “medicine” and “treatment”.

- **Individualized** - This term, in use for many years,(20) implies tailoring treatment to individual needs, taking account of contributory variables. It implies no assumptions about the methods used or sources of variability.
- **Personalized** - This term originally meant much the same as “individualized”.(21) However, in the 1980s it was applied to the use of genetic polymorphisms in preventive medicine, purportedly creating “medicine that will be more efficient and less burdensome for the community than the present mass system”.(22) It then started to be used to refer specifically to the supposed usefulness of genetic tests in predicting individual responses to treatment.(23)
- **Stratified** - The realization that purely genetic factors were insufficient in determining individual doses or predicting outcomes in most cases, coupled with the desire to use pharmacogenetics predictively, led to the idea of stratified medicine,(24) in which individuals would be grouped according to common characteristics, often a shared biomarker, rather than being treated individually.
- **Precision** - This term emerged in the 1990s.(25) However, it is imprecise, since one seeks accuracy and precision in drug therapy. Nevertheless, the meaning has converged with other terms, and is the current buzzword. A Committee of the US National Research Council defined personalized and precision medicine using the same words (26): “the tailoring of medical treatment to the individual characteristics of each patient”; they then contradicted themselves by saying that this means “the ability to classify individuals into subpopulations that differ in their susceptibility to a particular disease”.

Whichever term you prefer, and “individualized” is the least value-laden, recognition that the factors that produce variability are both non-genetic and genetic, endogenous and exogenous, suggests a new definition for them all: “tailoring of drug therapy to the needs of an individual

or group of individuals, informed by intrinsic genetic and non-genetic characteristics, lifestyle, and pertinent environmental factors”. There are four possible major applications of determining genetic variability:

- **Diagnosis** - This has been achieved for some rare conditions, exemplified by the 100,000 genome project.(27)
- **Dosage determination**- This has not been achieved for any drug. For example, none of 112 polymorphisms in 25 genes predicted opioid dosage requirements in patients with cancers.(28) Combining three polymorphisms and two non-genetic variables produced a model that explained only 67% of warfarin dosage variability;(29) if, as this result suggests, each factor explains on average 20% of the variability, it would take ten independent factors to explain 90% of variability.
- **Avoiding adverse drug reactions** - This has been achieved for single adverse reactions to a few drugs, e.g., abacavir.(30)
- **Targeting drugs for beneficial outcomes** - This has been achieved for some cancer chemotherapy agents.

Clinicians deal with variability in several ways:

- **Ignore it (one-size-fits-all)** - typically in preventive medicine, e.g., vaccines, hormonal contraceptives, the Polypill,(31) but also because trials often test only one dosage.
- **Titrate the dosage and monitor outcomes**(32) - generally poorly done because of lack of time, the difficulty of measuring true outcomes, and the inadequacies of biomarkers.(33)
- **Use computerized reminders** - often ignored because of alert fatigue.(34)

- *Use pharmacogenetics to target benefits and avoid harms* - still restricted in practice to a few cases such as targeted therapies in cancer; phenotype does not always reflect genotype (e.g., thiopurine metabolism (35)).

The proportional split for the above modalities to deal with patient variability (or ignore it) has been changing over the time but for sure ignoring the issue has been the dominant approach for variety of reasons and the pace of shift to MIPD has been very slow as described in the White paper by Darwich et al.(11)

POPULATION PHARMACOKINETIC/PHARMACODYNAMIC-GUIDED DOSING

The population approach in data analysis (mixed-effects modelling) has been increasingly applied to pharmacokinetics (PK) and pharmacodynamics (PD) during drug development and in clinical practice after 40 years since its introduction to the field of pharmacology.

Population pharmacokinetics is the study of variability in plasma drug concentration-time and drug effect-time profiles between individuals following drug administration.(36) The models analyze individual data, typically using compartmental models, whose individual parameters are related the population mean and its variability. The uniqueness of this approach is the fact that the variability in the data, can be explained by group or individual specific covariates.

Analysis of covariates in population pharmacokinetics has been more common than pharmacodynamics and can include demographic, pathophysiological and lifestyle variables. For a given dataset, a population pharmacokinetic model will describe a typical individual profile, whose variability can be explained by covariates, with remaining unexplained variability and random error.

Once established, population pharmacokinetic models can be used to inform dosing, by determining regimens from different levels of covariates that will achieve the same target

concentration. The aim is to reduce variability in target concentration. A population pharmacokinetic model can be used to guide dosing in two major ways; group and individualized dosing.(37) Group-guided dosing involves the use of covariates in a population pharmacokinetic model to predict the dose required to achieve a target concentration. The groups can be based on a categorical covariate, such as CYP enzyme genotype, and it is also possible to categorize continuous covariates depending on the effect of the covariate on the parameter. An important advantage of this approach is ease of implementation, depending on the number of groups, and there is no need to measure the response (concentration). There are examples of the use of this approach to inform dosage adjustment, based on the results of clinical trials, as recommended on the label.(38) There are also examples of this approach for clinical dosage recommendations for licensed drugs to improve benefit, particularly in special populations in which there may be off-label use. In general, population pharmacokinetics is suited to drugs with high pharmacokinetic variability and a narrow therapeutic index. Figure 1 is an example of the flow diagram for implementation of such an approach.(38)

INSERT FIGURE 1 HERE

Individual-guided dosing involves measurements such as the concentration of drug in plasma to individualize doses. Thus, the approach estimates individual pharmacokinetic parameters using a population pharmacokinetic model as prior information and then fine tunes it further with few individual measurements. Since this approach requires individual measurements, therapy can begin with group-informed dosing. This approach is also referred to as

therapeutic drug monitoring (TDM) and target concentration intervention and has been implemented in commercially and freely available or commercial software.

For a population pharmacokinetic model to be used to adjust doses in clinical practice, it must be developed appropriately and adequately validated. Such models should contain the most relevant physiological and biological attributes determining the drug's fate and should explain a substantial portion of observed variability. Hence, although attributes related to size and age (as the most commonly tested covariates), might be essential, they are not adequate. A population pharmacokinetic model can be validated internally, externally, or prospectively, to diagnose misspecifications.(39) Prospective evaluation can be included in studies designed to evaluate the potential benefit of the method, or device, of dosage adjustment or individualization over current practices. It should be noted that these models cannot address the impact of covariates which were not part of the original dataset.

BAYESIAN FEEDBACK AND DOSE ADJUSTMENT AS OPPOSED TO TRIAL AND ERROR

Bayesian theory provides a statistical framework to formalize the intuitive process of trial and error for dose optimization. In clinical practice, prior expectations about a drug's response at a given dose are updated by monitoring the patient for outcomes. A Bayesian dosing system works much the same. The set-up includes a prior model, a system patient data inputs, a search algorithm, means of outputting individualized parameter estimates from the model, and individual response predictions. The model provides the prior population estimates for parameter values. Individualized estimates of the parameters are usually obtained by searching for the parameter values that satisfy both the observed data for each individual and expected prior values by minimizing a maximum a-posteriori (MAP) objective function.(40)

The prior is usually fixed, with the predictions updated based on new data (exception in (41)). Time weighting penalties are often incorporated to down-weight older observations. Most methods provide point estimates of parameters rather than a full Bayesian posterior.

Implementation - Bayesian forecasting tools for dose individualization were first proposed by Sheiner et al.(40; 42) and have since been developed for several therapies.(43-45) Many are developed as software,(46; 47) some use non-parametric methods.(48) Increasingly, web-based dashboards(49-52) and integrated clinical decision-support systems (CDSSs) in electronic health records (EHRs) or e-prescribing systems are being proposed.(50)

Bayesian forecasting has traditionally been linked with TDM and more recently MIPD. In TDM, Bayesian systems are often used to predict the plasma concentrations of drugs with a narrow therapeutic index such as antibiotics,(53; 54) antifungals,(55) immunosuppressants used for organ transplantation and other indications(44; 56; 57) and oncology drugs(17; 58; 59) and in some specific population groups.(11) Bayesian dosing has also been applied to pharmacodynamic endpoints, including INR monitoring for warfarin.(60; 61)

Bayesian dosing tools have not been widely implemented in healthcare. Free downloadable software are often developed in academic settings with sporadic uptake. Commercial software can be scaled more consistently to a larger userbase but are often expensive, require support, local expertise, and buy-in from funders. The widespread implementation of Bayesian dosing tools faces several challenges(8; 11; 12; 62; 63). Mainly, the regulatory requirements associated with software as a medical device (SaMD) (learning devices are particularly problematic,(64)), and limited prospective studies evaluating impact on patient outcomes. If clinical and economic benefits can be demonstrated in well-conducted evidence-generating studies, then funding bodies and health authorities will have more incentive to support implementation.

Scalability and other technical issues - In theory, if the prior model is sufficiently informative and scalable across populations, a Bayesian forecasting tool for a given drug could predict response in multiple clinical settings. In practice, this is difficult to achieve. The prior will usually be an empirical model, often developed using data from a particular population that may not predict well into other populations. The posterior (MAP) estimates of the parameters can be thought of as a weighted average of the prior and the likelihood of the data, if the prior is uninformative or biased the Bayesian system would be expected to struggle. Sampling designs for optimal Bayesian parameter estimation are not routinely explored so the number and frequency of response observations to accurately estimate individual parameters for a patient are often not known. This becomes particularly important with more complex models suggesting that a Bayesian dosing system will not be clinically practical for scenarios where observations are collected infrequently (e.g., three monthly clinic visits).

Ongoing Efforts and Future Direction - Bayesian dosing systems have never been short of interesting technical advances. Artificial intelligence/machine learning are no longer computationally daunting and have already been implemented in some Bayesian algorithms. Technical innovations suggested over 20 years ago are long overdue for re-examination, including the use of an updating prior model, and a move away from point estimates (MAP) for parameter estimation to a full Bayesian Posterior.

The challenge for Bayesian dosing moving forward is clinical acceptability. Indifference from the medical and healthcare community is understandable. Pharmacometrics is completely absent from medical school programs. Commercial providers rely largely on marketing to sell the concept. Until Bayesian dosing is accepted by the healthcare community as decision-support tools for some drugs, until funders see the economic and clinical benefits, and until regulatory agencies clarify the status of these systems from a regulatory/legal

perspective, the future remains uncertain. Integration of Bayesian tools into EHRs and CDSS available at scale is a reasonable goal.

PATIENT CHARACTERIZATION STRATEGIES: GENOTYPING, ENDOGENOUS PROBES AND LIQUID BIOPSY

The difficulties in setting up multiple TDM assays for each specific drug has led many researchers to follow a different avenue that is less drug-dependent. The philosophy behind this is to define the most influential patient characteristics that determine the fate of drugs in the body and then use a select set of these, in combination with modelling to optimize drug therapy. Various approaches are currently adopted. Genotyping for drug metabolizing enzymes, transporters and receptors is the first line of such common targets and they can explain large differences in activity; for example, CYP2C9*2 has reduced activity and CYP3A5*3 is inactive with frequencies of approximately 11% and 85% in Caucasians, respectively.(65; 66) When single nucleotide polymorphism (SNP) occurs in an enzyme or transporter dominant in a key clearance step, it can affect drug exposure, efficacy and toxicity profiles. However, population variability is better reflected by phenotyping. Administration of a cocktail of specific exogenous substrates (e.g., Cooperstown cocktail) is used as a phenotyping tool in patients, but the approach is invasive and often requires ethical approval. Recent efforts have therefore been directed to identifying, characterizing, and validating a range of endogenous compounds as selective substrates for individual enzymes and transporters. These include endogenous metabolites or metabolite/parent ratios in plasma or urine. Examples include plasma 4 β -hydroxycholesterol and urine 6 β -hydroxycortisol/cortisol ratio for CYP3A activity, and plasma coproporphyrin I for OATP1B function.(67) Efforts to develop models for such endogenous compounds are currently underway with a view of applying this to DDI risk assessment and patient selection for clinical trials.(68) Only a

limited number of sufficiently selective biomarkers have so far been identified(67) and these compounds tend to explain only a fraction of the variability in activity.(69) Robust liquid biopsy assays were proposed to complement these techniques

Liquid biopsy involves collection of biofluid (e.g., blood or urine) from patients at defined intervals, followed by extraction and characterization of exosomes. Exosomes are small extracellular vesicles (~50-100 nm) constitutively released into the bloodstream (or urine) via exocytosis by different tissues, at variable rates under physiological or pathological conditions. These vesicles enclose functional transmembrane and non-membrane proteins and nucleic acids sampled from the cellular biochemical pool. They are therefore believed to reflect the functional state of their tissue of origin. Historically, exosomes have been used extensively in disease biomarker research.(70; 71) More recently, exosome data can be used to construct a snapshot of enzymes expressed in a particular tissue.(14; 15)

Despite interest in integrating liquid biopsy with PK/PD modelling, the area of exosomal isolation and characterization remains a specialist one. Isolation of exosomes employs various methods (e.g., ultracentrifugation, immunocapture or polymer-based precipitation), which require optimization for the type of tissue or biofluid, followed by confirmation with electron microscopy, size distribution and immunolabeling of particular surface proteins (e.g., CD63 or CD81). Finally, the exosomal ‘cargo’ is analyzed, which requires genotyping and multi-‘omic’ methods to discern quantitatively the composition of nucleic acids and proteins within the vesicles.(68) Further, validation is required for each protein. Available literature(14; 72; 73) demonstrated that a wide range of enzymes, such as CYPs, UGTs and SULTs, are shed in plasma exosomes. Several transporters (e.g., P-gp, BCRP and OCTN2) are also present in plasma and urine.(74-76) Quantitative correlations have recently been established between exosomal and liver tissue expression of CYPs and UGTs,(14; 77) and current efforts are extending this to transporters. Establishing such assays enables the use of

biofluid analysis to support pharmacological phenotyping in disease and special populations. The utility and applications of this multi-faceted strategy remain to be explored. It is envisaged that incorporation of such new individual data into EHR systems will take a long time. This is based on the experience with the genetic information which have been available for over 2 decades and yet they are not routine part of any EHR systems beyond the leading university hospitals.(11) Nonetheless, the infrastructure to implement such information as part of creating a “Virtual Twin” of a patient is in place and can become operationalized when the data become part of EHR’s as demonstrated in Figure 2.(78)

INSERT FIGURE 2 HERE

INCREASING NEED FOR MIPD TOOLS IN CLINICAL PRACTICE

Clinicians nowadays are expected to process a significant amount of patient information related to diagnostics, such as medical imaging, laboratory tests, and previous clinical presentations, and to identify multiple risk factors influencing drug efficacy and safety, including pharmacogenomics, DDIs, diet, organ impairment, age, and functional status of the patient. Rapid, optimal integration of all this information, and ‘softer’ factors such as drug formulary recommendations and patient/care-giver choice, is crucial for making prescribing decisions that result in high-quality patient care. This can be overwhelming, mistakes are easily made, and ADRs may result.(79-81)

Complex drug-drug-gene-disease interactions (DDGDI) are intricately complicated clinical situations that cannot be identified prospectively but are documented retrospectively as case-reports of severe ADRs. A good example is the tyrosine kinase inhibitor (TKI) class of drugs,

which improve survival rates for a variety of cancers. However, many patients experience multiple intolerable adverse effects – the TKI must be temporarily stopped or replaced, which in turn increases the risk of developing drug resistance. Many other patients are non-responders initially or develop drug resistance during treatment due to genetic factors, such as TK mutations or polymorphisms of drug metabolizing enzymes and transporters, or via DDIs or dietary changes. Another example of a complex DDGDI is opioid intoxication on low-dose codeine in ultra-rapid metabolizers for CYP2D6 (metabolic pathway producing morphine) in combination with inhibition of CYP3A and acute renal failure in patients who are opioid naive.(82) The addition of subsequent variabilities related to μ -opioid receptor mutations could also explain rare cases of codeine toxicity.

These ADRs contradict the “one-size-fits-all” dosing approach supported by an allegedly large therapeutic window for many drugs. Direct oral anticoagulants (DOACs) and the anti-platelet drugs (P2Y₁₂ receptor antagonists) are classic examples. Cardiovascular patients who require these treatments are generally older and more medically complex than previously, with multiple co-morbidities and polypharmacy. Despite an established relationship between DAOC exposure and risk of major bleeding,(83) few formulations allow dose tailoring e.g., apixaban. To date, there are no clinical tools available for selecting the “ideal” DOAC or anti-platelet drug and optimal dose. The management becomes even more complex when the link between PK/PD and clinical outcomes is distorted by clinical conditions e.g., the relationship between platelet inhibition by clopidogrel and the occurrence of ischemic events is influenced by background cardiovascular risk.(84) In practice, a “poor response” to clopidogrel is clinically relevant in higher risk cardiovascular patients who may be the sole benefactors of dose adjustment or drug change. Therefore, patient characteristics and conditions are an integral to drug-related clinical prognosis.

Predicting optimal drug doses in individual patients *a priori* represents the Holy Grail for physicians in drug therapy. Smart, easy to use and clinically validated MIPD tools would be of tremendous value in improving patient care. This can be facilitated by through integration into EHRs. Such tools could combine clinical and demographic information and other biomarkers, electronic prescriptions and, for example, a physiologically-based pharmacokinetic (PBPK) model with fully validated drug and population databases.(85) This requires validation in clinical settings in sufficiently large cohorts. Clinical trials are currently underway to validate a PBPK-based MIPD approach for antithrombotic drug management(86), although it should be recognized that this approach may not always be feasible. Here there are a lot of learnings from evidence generation, evaluation, implementation research in healthcare, sociotechnical systems research, health systems engineering and health economics that can inform and further develop this process.(87-89) Finally, clinical education and engagement (such as participatory methods) on MIPD would ensure accurate and critical interpretation of dose predictions, and implementation at the point of care. Indeed, multidisciplinary efforts are needed to ensure widespread implementation of these approaches.

IMPLEMENTATION INTO ELECTRONIC HEALTH RECORDS

Implementation of MIPD into EHRs has been discussed in the literature.(3; 11; 12; 90; 91) There are some stand-alone solutions, and medical dosing devices can be integrated into EHRs.(12; 90; 91) Stand-alone systems have a usability problem since the prescriber must enter all patient data manually. Linkage to EHRs in which structured patient data are available would overcome these problems. Depending on the model, the availability of data varies. Most EHRs store structured data for demographics, other drug treatments, and various laboratory parameters for kidney, liver function etc. Genetic patient information is still rare in

EHRs and standards are needed to structure the information. There are ongoing efforts in the area of semantic interoperability (ability of computer systems to share data with unmistakable meaning) through standardization of, for example genetic information, such as HL7 FHIR.(92) These type of initiatives are important enablers for precision medicine in clinical practice. Although standardization is an important part of information sharing across systems, it is likely that this will only be relevant for a limited core of medical data structures as the field of medicine is heterogenous and constantly evolving. An alternative approach that is being developed within the Swedish Origo programme, is the development of a language for developing semantic data structures within a distributed non-profit and open source infrastructure, thereby allowing accelerated user-defined data structure and sharing.(93) This approach may overcome some of the issues around standardization for interoperability and could be a potential enabler for MIPD in healthcare.

CDSSs for drug treatment are today frequently implemented into EHRs. However, their outcome regarding improvement of healthcare quality and outcome is still unclear.(94; 95) CDSS are based on knowledge bases of various types, such as DDIs, pregnancy, breastfeeding, and renal impairment. These knowledgebases are created as individual databases and alert prescribers based on the content of the specific knowledgebase in relation to the patient's parameters. Some databases exist for pharmacogenomics.(96) However, these are rarely implemented in EHRs. All knowledgebases give advice to alter/stagger doses, or switch drug. CDSS can create alert fatigue for the users due to extensive warnings.(97)

The existence of various CDSSs within EHRs has to be taken into account whenever a MIPD system is integrated. If the MIPD model has taken kidney function or concomitant drug treatment into account, it must be clear for the user that the possible alert from the renal knowledgebase should be ignored.

Depending on the model used, the dosing suggestion could replace the use of some already existing CDSSs. MIPD suggestions for dosing based on pharmacogenetics, kidney and liver function and concomitant drug treatment could replace the information and possible alerts from at least three different CDSSs. The suggested dose would have been calculated based on all these parameters and being presented to the prescriber as one recommendation only, thereby diminishing the need for other warnings from the individual knowledge bases. This would require algorithms in the EHR that would eliminate firing alerts from specific knowledge bases whenever the MIPD based dose suggestion already included these patient specific parameters.

CDSS research has shown that recommendations how to handle the patients' drug treatment are preferred to simple messages containing only information about what not to do. It is therefore of importance how these recommendations would be communicated through the CDSS. With increasing availability of patient data, the integration of these tools are becoming more feasible.

AN INDUSTRIAL PERSPECTIVE ON MIPD DURING DRUG DEVELOPMENT

Optimal use of drugs is desired by the pharmaceutical industry from both an altruistic and economic perspective. Thus, there is a vested interest in getting the dose right which is strengthened even more based on the ongoing debate over the last 10 years by policy makers over the increasing cost of health care (98) and possibility of an "outcome-based compensations" model of any intervention (also called "pay-for-performance").(99) It is assumed that the approach increases quality of care and reduce healthcare costs by removing the expenditure on cases where the intervention does not provide value, including individualizing the drug treatment.

It has been routine for industry to collect exposure-response data in drug development.(100) In addition, drug development routinely characterizes the pharmacokinetic profile of the drug and some of the intrinsic and extrinsic factors that influence the profile focusing on those that are mandated to have labeling information (e.g., pediatric)(34) or suggested in a regulatory guidance (e.g., hepatic and renal insufficiency).(101) Yet, dosing recommendations for these patient groups are frequently lacking. A survey of 59 new molecular entities approved in 2013/2014 found labeling recommendations lacking for such populations over 60% of the time; it is recognized further that information for the pediatric population is typically not available at the time of first approval.(102) Usually when there are dose recommendations, they reflect only a single factor and leave the prescriber guessing as how to integrate the information provided.

While the field of pharmacokinetics has made significant strides in its ability to produce predictive models (e.g., DDIs), much more can be done. Development of predictive models can be facilitated by pooling of data across compounds, done recently for pediatric patients.(103) CDSSs could allow the integration of various factors into dosing recommendations to better serve complex patients and make paper labels obsolete. Advances in liquid biopsy/exosome science offer the ability to characterize metabolic pathways(14) and this may facilitate obtaining information in patient populations where it was previously too difficult to obtain such information (e.g., pregnancy).

Most of the promise noted above hinges on the pooling of data and much of that data resides in industry. To date there have been few, if any, industry wide efforts to pool data to facilitate dose recommendations. For example, a proposal to create a framework for dosing recommendations in specific populations using M&S based on data from prior drugs with similar clearance mechanisms was made through the Innovative Medicines Initiative(104; 105). However, the proposal failed to receive the necessary industrial support and therefore

did not go forward. Efforts like this may fail because individual companies do not see return on the investment and fear that competitors will not take part but will reap the rewards. To overcome this, regulatory bodies may want to consider incentivizing such efforts and making participation mandatory. Further, before full benefits can be achieved, questions such as, when is a model sufficiently predictive, need to be considered. A joint effort by industry and regulatory agencies is consistent with efforts to increase diversity of patients in clinical trials(106), and would go a long way to achieving optimal drug use in all patients.

REVISITING HEALTH ECONOMICS: THE FALSE ECONOMY OF ONE-SIZE-FITS-ALL DOSING

Medicines are the most common health intervention and represent a major portion of global health budgets.(107) Medicines also have the greatest potential to improve human health and quality of life through the treatment or prevention of human illness and suffering. Every health intervention has a cost which needs to be weighed against benefits and harms. There is an increased economic burden of medicines-related harm in many health systems with negative impact on patients' quality of life.(108-110) This prompted the World Health Organization (WHO) to name the Third Global Patient Safety Challenge as *Medication without harm*.(110) The majority of medication-related harms are preventable, and the WHO Global Patient Safety Challenge aims to reduce preventable harms caused by medicines by 50% over 5 years. Of these preventable medicine-related harms, over- and under-dosing of medicines account for a sizeable portion.(111; 112) Judicious drug selection and dose individualization can lead to improved health outcomes, preventing medication-related harms and reducing the economic burden.

The appropriate use of medicines should always be guided by the best evidence on efficacy, effectiveness and cost-effectiveness.(113) This evidence framework for decision making about medicines assumes that the medicine is administered at a dose intensity the allows the individual to achieve the best outcomes. In reality, most treatments are not optimally dosed in all patients but use a one-dose-fits-all approach. The economic impact of this involves understanding the costs associated with individualizing drug selection and dosing and needs alongside the missed opportunity to realize the true value of medicines by using such an approach.

The value of drug treatment - The value that a medicine provides is a reflection of the cost to the health system and the benefits (and harms) it provides in the broader population.(114) These data are often derived or extrapolated using modelling approaches from controlled clinical trials conducted during development. Reasonable assumptions about the disease process, cost of care and clinical pharmacology of the drug are combined to estimate the (economic) value that a medicine provides during treatment.(115) A key assumption is that the medicine is administered at the right dose regimen. The reality is that in the post-marketing stage, where a medicine is used in the wider patient population, there is increased variability in response.(116) This is most evident when the medicine is used with a fixed dosing strategy without any dose adjustment based on patient characteristics. This means that the expected benefit of the medicine in wider community is not realized.(117)

The false economy of One-Size-Fit-All - National medicines policies around the world provide a foundation for medicines regulation frameworks.(118) These policies also acknowledge the need for an economically viable and responsible pharmaceutical industry as a partner in healthcare. This recognises that pharmaceutical sponsors bring medicines to market and their profits are not only distributed to shareholders but also reinvested in research and development into new therapeutic agents to improve human health.(119) From a

pharmaceutical sponsor's perspective, developing a new medicine with a one-size-fits-all dosing strategy might seem an economically favourable and efficient therapeutic strategy. In many cases generating evidence of safety and efficacy, and even cost-effectiveness, is more straightforward if the new medicine is administered at one or a few dose level(s). Less formulation work and fewer trials lead to lower development costs and more importantly faster route to market.(119) Physicians also tend to prefer medicines that are "easy to prescribe". Yet this strategy does not ensure the best/optimal outcomes for each patient. After wrestling over two decades with idea of considering genetics and ethnicity in adjusting the dose we understand that strength and limitations of associating variability in response to medicines to such sources.(120-122) There is now a more balanced view on the molecular basis of variability with less hype around the potential.(123) Differences in genetics(124) alongside age, body size, diet, comorbidities, organ impairment, concomitant medicines and ethnicity(59; 121; 122) are just some of the factors that have a significant impact on variability and dosing. The implications of a fixed dosing approach mean that some people may be unnecessarily harmed by the medicine or fail to adequately respond – both of which will lead to treatment cessation.(124) Treatment persistence is economically favourable for the patient, health system and the pharmaceutical sponsor.(125)

The economic benefits of medicine use is driven by benefits and harms to populations, but we treat individual patients with medicines and specific doses.(117; 124) Empirical drug dosing strategies are based on the typical individual, these are the patients included in the pivotal clinical trials. Much has been written about the limitations of clinical trials to guide dosing.(116; 124) The focus on the typical patients that gives rise to fixed dosage regimens ignores the wealth of real world data that supports the need to individualize dosing.(117; 124)

"Imprecision" medicine represents low value care.(124; 126) This means that despite the expense of drug treatment, an investment in health outcomes, the value is not realised.

Medicines use and dose optimization must also embrace shared-decision making principles to support the preferences, beliefs, attitudes, knowledge and social context for individual patient. (127)

Cost of “imprecision” medicine use in older people - Older people most commonly use medicines.(121) Many older patients have multiple comorbidities and polypharmacy.(128) Along with aged-related changes in the clinical pharmacology of medicines these factors put older people at great risk of preventable medication-related harms.(121; 128; 129) The impact of the ageing population across the globe has been identified as a major economic challenge for healthcare. The imprecise manner in which medicines are used creates an added burden of preventable harm and low value care.(121; 128) Older people are among the most vulnerable to the potential harms of medicines which can add considerable cost to the health system.(129) Integrating knowledge of clinical pharmacology, physiology(121; 128) and the impact of disease can guide individualized dosing regimens in elderly.(129) This has considerable potential to ensure that when medicines are initiated and carefully monitored clinicians can provide high value care.

A REGULATORY PERSPECTIVE ON MIPD

A long-standing goal of regulators is to ensure that the right drug is given to the right patient at the right dose and time. This is the contemporary concept of precision medicine and has become increasingly possible with regard to matching the right drug to the right patient. It is common in drug development to leverage the power of the human genome to target specific diseases. Cancer therapies that target specific genetic changes in tumors have benefited the most, going back more than two decades when FDA approved rituximab(130). Since then, more than 150 indications for targeted therapies in 28 cancer types have been approved by

FDA.(131) In 2018, precision medicines represented 42% of all new drug approvals and several diseases have benefited.

In contrast, precision medicine has outpaced MIPD. Regulators play a major role in advancing innovative science, MIPD has been embedded in several FDA initiatives such as the critical path initiative and more than 10 clinical pharmacology Guidance for Industry. More recently, the 21st Century Cures Act (2016) advocates for innovation in individualizing drug therapies. The Prescription Drug User Fee Act (PDUFA, 2018-2022)(132) also has a deliverable of advancing model-informed drug development (MIDD), including MIPD.(133)

MIPD Regulatory Framework during Drug Development - Unlike landmark regulatory legislation of 1938 that set in place the Federal Food, Drug and Cosmetic (FD&C) Act that required industry to demonstrate drug safety, and the Kefauver-Harris Drug Amendments of 1962 required industry to prove efficacy, there are no regulations that require industry to enable precision dosing during drug development. The current practice in drug development, expected and supported by regulatory agencies, is to bin patients into subgroups defined by factors that influence pharmacokinetics (e.g., renal impairment, elderly, smokers, body weight, phenotype) as if all patients in the respective subgroups are identical. Precision dosing in these so-called “special populations” amounts to adjusting standard population doses based on model-driven matching of pharmacokinetic exposure with the critical assumption of similar exposure-response relationships across the individual subgroups. MIPD in this context has been hailed as the “age of individualization”. On occasion, some drug development programs have enabled precision dosing using pharmacodynamics as a guide. For example, FDA recently approved a recombinant coagulation factor VIII prophylactic treatment for hemophilia A with a companion PK CDSS that individualized dose based on trough concentrations of drug to achieve a target clotting activity.

MIPD for Regulatory Framework for the Real World - MIPD promises to individualize dosing at the point-of-use in healthcare. Here, the regulatory oversight of MIPD as CDSS is a moving target. A draft guidance has been issued by FDA in 2019, laying out potential pathways to regulatory approval or clearance. Because of this uncertainty, the pace of development of commercial CDSS for MIPD has been slow despite the use and demonstrable effect of TDM for more than 40 years. The challenge today is that FDA interprets CDSS as a device under the FD&C Act because the software informs clinical management for serious or critical situations or conditions and that clinicians are not able to independently evaluate the basis for the CDSS recommendations. The factors that regulators consider in making benefit-risk determinations of CDSS are, in the efficacy category, the type and magnitude of the benefits and the probability of a patient experiencing one or more benefits. On the safety side, regulators are interested in the extent of probable risks including the severity, type and rates of harmful events associated with the CDSS.

ADDRESSING THE BARRIERS

Timely access to patient-specific information to guide drug dosing has been a major barrier to achieving precision dosing. With the considerable expansion of EHRs, clinicians now have increased access to information about patient factors such as age, weight, sex, organ function, relevant genotype, concomitant medicines and disease severity which can be used to better tailor drug dosing. Being able to access relevant biomarker information to monitor and adjust doses according to an individual's pharmacological response in an evidence-based manner is vital to achieve optimal outcomes and will ensure that the value of drug therapy can be realized. Combining these data into appropriately developed and evaluated pharmacokinetic-pharmacokinetic models, and other types of modelling regimes such as AI/ML, will provide

the step change needed to allow large scale tailoring of drug doses to meet the needs of individual patients.

SUMMARY POINTS

- Industry, regulators and clinicians recognize the need for MIPD supported by CDSS. However, it is unnecessary to apply MIPD to every drug and every patient.
- The community must delineate well-defined situations where MIPD is important and considerably more effective than traditional dosing.
- Precision medicine in oncology has transform the standard of care in less than a decade. The continued evolution of computer technology, regulatory policy and clinician adoption may find precision dosing transforming the standard of care in the same way.
- Medication-related harms are a significant burden on healthcare and in many cases preventable. MIPD can lead to improved health outcomes, preventing medication-related harms and reducing the economic burden.
- The economic cost of implementing MIPD strategies to improve the initiation and monitoring of medications should be weighed against the direct economic burden to healthcare of preventable medication-related harm.
- Widespread use of MIPD requires a multidisciplinary approach to meet challenges in evidence generation, implementation and systematic use.

FUTURE ISSUES

- A shift from “drug-specific” assays to non-drug specific “patient-characterization” will be a general trend over the next decade, where patient characterization goes

beyond genetics and addresses proteomics and other elements defining the biology and physiology of the system at each stage of health and disease in each patient.

- The application of MIPD will reach its full potential beyond the classical examples in TDM. It is envisioned that personalized predictive models will be used for precision dosing based on pharmacodynamic targets and patient outcomes. For this, a greater understanding of mechanisms and variability of disease and treatment is needed, as well as the translation to clinical outcomes.
- Artificial intelligence and machine learning is entering the arena of precision dosing. This could be a potential game changer for the utilization of real world patient and healthcare data.
- The integration of CDSSs for MIPD and EHRs is an important enabler for widespread use. Efforts in standardization, interoperability and information and communications technology will be important for this.
- Evidence generation and implementation of MIPD in healthcare will require multidisciplinary efforts and collaborations between healthcare, academia, regulators, patients and other key stakeholders.

SIDEBAR

Integration of CDSSs which are capable of automated communication with EHR systems for MIPD is easy. However, what is often forgotten is the availability, quality and understanding of relevant information that characterizes the patient, treatment and outcomes. Still, genetic information about patients is missing in most EHR systems after decades of debate over their usefulness and value. Hence the adoption of additional –omics information will take time for EHR integration, despite the fact that scalability of these measures is not an issue, unlike the TDM assays which are specific to a single drug. Approval of a “Dosing Strategy” as opposed

to approval of certain dosage regimens will make it inevitable to have the MIPD tool as a companion to the drug itself through the process of new drug approval.

TERMS AND DEFINITIONS

- ADR: adverse drug reaction.
- CDSS: clinical decision support system.
- EHR: electronic health record.
- MIDD: model-informed drug development.
- MIPD: model-informed precision dosing, prediction methods for optimizing treatment efficacy/harm balance, based on individual characteristics of the patient, disease, treatment and/or other factors.
- PBPK: physiologically-based pharmacokinetics.
- PD: pharmacodynamics.
- PK: pharmacokinetics.
- Precision dosing: tailoring of drug therapy to the needs of an individual, or group, informed by intrinsic, lifestyle, and pertinent environmental factors
- Precision medicine: the tailoring of medical treatment to the individual characteristics of each patient.
- SaMD: software as a medical device.
- Semantic interoperability: the ability of computer systems to share data with unmistakable meaning.
- Virtual twin: a computer-based simulation model that integrates physiological and biological information to mimic an individual patient.

701

702 **REFERENCE ANNOTATIONS**

703 1. Highlighting the state-of-the-art and future direction of MIPD based on expert
704 meeting in 2016.(11)

705 2. Review on the practices and potential of MIPD in oncology.(59)

706

707 **DISCLOSURE STATEMENT**

708 TP and ARH are employed part-time by Certara, a company that develops and supplies
709 modelling and simulation software and services to the pharmaceutical industry.

LITERATURE CITED

1. Organization WH. 2017. Medication Without Harm - Global Patient Safety Challenge on Medication Safety. Geneva
2. Polasek TM, Kirkpatrick CMJ, Rostami-Hodjegan A. 2019. Precision dosing to avoid adverse drug reactions. *Ther Adv Drug Saf* 10:2042098619894147
3. Gonzalez D, Rao GG, Bailey SC, Brouwer KLR, Cao Y, et al. 2017. Precision Dosing: Public Health Need, Proposed Framework, and Anticipated Impact. *Clin Transl Sci* 10:443-54
4. Polasek TM, Shakib S, Rostami-Hodjegan A. 2018. Precision dosing in clinical medicine: present and future. *Expert Rev Clin Pharmacol* 11:743-6
5. Vinks AA, Emoto C, Fukuda T. 2015. Modeling and simulation in pediatric drug therapy: Application of pharmacometrics to define the right dose for children. *Clin Pharmacol Ther* 98:298-308
6. Sheiner LB. 1969. Computer-aided long-term anticoagulation therapy. *Comput Biomed Res* 2:507-18
7. Jelliffe RW. 1969. Administration of digoxin. *Dis Chest* 56:56-60
8. Wright DFB, Martin JH, Cremers S. 2019. Spotlight Commentary: Model-informed precision dosing must demonstrate improved patient outcomes. *Br J Clin Pharmacol* 85:2238-40
9. Polasek TM, Rayner CR, Peck RW, Rowland A, Kimko H, Rostami-Hodjegan A. 2019. Toward Dynamic Prescribing Information: Codevelopment of Companion Model-Informed Precision Dosing Tools in Drug Development. *Clin Pharmacol Drug Dev* 8:418-25
10. House TW. 2015. *The Precision Medicine Initiative*.
<https://obamawhitehouse.archives.gov/precision-medicine>
11. Darwich AS, Ogungbenro K, Vinks AA, Powell JR, Reny JL, et al. 2017. Why has model-informed precision dosing not yet become common clinical reality? lessons from the past and a roadmap for the future. *Clinical pharmacology and therapeutics* 101:646-56
12. Polasek TM, Rostami-Hodjegan A, Yim D-S, Jamei M, Lee H, et al. 2019. What Does it Take to Make Model-Informed Precision Dosing Common Practice? Report from the 1st Asian Symposium on Precision Dosing. *The AAPS journal* 21:17

13. Polasek TM, Tucker GT, Sorich MJ, Wiese MD, Mohan T, et al. 2018. Prediction of olanzapine exposure in individual patients using physiologically based pharmacokinetic modelling and simulation. *Br J Clin Pharmacol* 84:462-76
14. Rowland A, Ruanglertboon W, van Dyk M, Wijayakumara D, Wood LS, et al. 2019. Plasma extracellular nanovesicle (exosome)-derived biomarkers for drug metabolism pathways: a novel approach to characterize variability in drug exposure. *Br J Clin Pharmacol* 85:216-26
15. Rostami-Hodjegan A AB, and Rothman JE. 2019.
16. van der Graaf PH. 2019. Pharmacometrics and/or Systems Pharmacology. *CPT Pharmacometrics Syst Pharmacol* 8:331-2
17. Zhang J, Zhou F, Qi H, Ni H, Hu Q, et al. 2019. Randomized study of individualized pharmacokinetically-guided dosing of paclitaxel compared with body-surface area dosing in Chinese patients with advanced non-small cell lung cancer. *Br J Clin Pharmacol* 85:2292-301
18. Smith FE, Rawlins MD. 1973. *Variability in Human Drug Response*. London: Butterworths
19. Richens A. 1974. Review of Variability in Human Drug Response. *Proceedings of the Royal Society of Medicine* 67:520
20. Rogoff B. 1954. Rheumatoid arthritis; the need for individualized therapy. *Mo Med* 51:1001-2
21. Koos EL. 1947. What society demands of the nurse. *American Journal of Nursing* 47:306-7
22. Dausset J. 1981. The major histocompatibility complex in man. *Science* 213:1469-74
23. Langreth R, Waldholz M. 1999. New era of personalized medicine: targeting drugs for each unique genetic profile. *Oncologist* 4:426-7
24. Trusheim MR, Berndt ER, Douglas FL. 2007. Stratified medicine: strategic and economic implications of combining drugs and clinical biomarkers. *Nat Rev Drug Discov* 6:287-93
25. Wasi P. 1997. Human genomics: implications for health. *Southeast Asian J Trop Med Public Health* 28 Suppl 2:19-24
26. Disease NRCUCoAffDaNTTo. 2011. *Toward Precision Medicine: Building a Knowledge Network for Biomedical Research and a New Taxonomy of Disease*. Washington DC: National Academies Press

- 775 27. Turnbull C, Scott RH, Thomas E, Jones L, Murugaesu N, et al. 2018. The 100 000
776 Genomes Project: bringing whole genome sequencing to the NHS. *BMJ* 361:k1687
- 777 28. Klepstad P, Fladvad T, Skorpen F, Bjordal K, Caraceni A, et al. 2011. Influence from
778 genetic variability on opioid use for cancer pain: a European genetic association study
779 of 2294 cancer pain patients. *Pain* 152:1139-45
- 780 29. Gaikwad T, Ghosh K, Avery P, Kamali F, Shetty S. 2018. Warfarin Dose Model for
781 the Prediction of Stable Maintenance Dose in Indian Patients. *Clin Appl Thromb*
782 *Hemost* 24:353-9
- 783 30. Sousa-Pinto B, Pinto-Ramos J, Correia C, Goncalves-Costa G, Gomes L, et al. 2015.
784 Pharmacogenetics of abacavir hypersensitivity: A systematic review and meta-
785 analysis of the association with HLA-B*57:01. *J Allergy Clin Immunol* 136:1092-4 e3
- 786 31. Wald NJ, Law MR. 2003. A strategy to reduce cardiovascular disease by more than
787 80%. *BMJ* 326:1419
- 788 32. Glasziou P, Irwig L, Aronson JK. 2008. *Evidence-based Medical Monitoring: From*
789 *Principles to Practice*. Oxford: Blackwell Publishing/BMJ Books
- 790 33. Aronson JK, Ferner RE. 2017. Biomarkers-A General Review. *Curr Protoc*
791 *Pharmacol* 76:9 23 1-9 17
- 792 34. 21 UFC-CoFRT.
793 <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=201.56>
- 794 35. Zimdahl Kahlin A, Helander S, Skoglund K, Soderkvist P, Martensson LG, Appell
795 ML. 2019. Comprehensive study of thiopurine methyltransferase genotype,
796 phenotype, and genotype-phenotype discrepancies in Sweden. *Biochem Pharmacol*
797 164:263-72
- 798 36. Aarons L. 1991. Population pharmacokinetics: theory and practice. *Br J Clin*
799 *Pharmacol* 32:669-70
- 800 37. Holford NH, Buclin T. 2012. Safe and effective variability-a criterion for dose
801 individualization. *Ther Drug Monit* 34:565-8
- 802 38. Wicha SG, Kees MG, Solms A, Minichmayr IK, Kratzer A, Kloft C. 2015. TDMx: a
803 novel web-based open-access support tool for optimising antimicrobial dosing
804 regimens in clinical routine. *Int J Antimicrob Agents* 45:442-4
- 805 39. Ince I, de Wildt SN, Tibboel D, Danhof M, Knibbe CA. 2009. Tailor-made drug
806 treatment for children: creation of an infrastructure for data-sharing and population
807 PK-PD modeling. *Drug Discov Today* 14:316-20

- 808 40. Sheiner LB, Beal S, Rosenberg B, Marathe VV. 1979. Forecasting individual
809 pharmacokinetics. *Clin Pharmacol Ther* 26:294-305
- 810 41. Duffull SB, Begg EJ, Robinson BA, Deely JJ. 1997. A sequential Bayesian algorithm
811 for dose individualisation of carboplatin. *Cancer chemotherapy and pharmacology*
812 39:317-26
- 813 42. Sheiner LB, Rosenberg B, Melmon KL. 1972. Modelling of individual
814 pharmacokinetics for computer-aided drug dosage. *Comput Biomed Res* 5:411-59
- 815 43. Thomson AH, Whiting B. 1992. Bayesian parameter estimation and population
816 pharmacokinetics. *Clin Pharmacokinet* 22:447-67
- 817 44. Staatz CE, Tett SE. 2011. Maximum a posteriori Bayesian estimation of
818 mycophenolic Acid area under the concentration-time curve: is this clinically useful
819 for dosage prediction yet? *Clin Pharmacokinet* 50:759-72
- 820 45. Turner RB, Kojiro K, Shephard EA, Won R, Chang E, et al. 2018. Review and
821 Validation of Bayesian Dose-Optimizing Software and Equations for Calculation of
822 the Vancomycin Area Under the Curve in Critically Ill Patients. *Pharmacotherapy*
823 38:1174-83
- 824 46. Mediware. <http://www.mediware.cz/en/mwpharm/>
- 825 47. DoseMeRx. <https://doseme-rx.com/>
- 826 48. BestDose. <http://www.lapk.org/bestdose.php>
- 827 49. Tucuxi. <http://www.tucuxi.ch/>
- 828 50. InsightRX. <https://www.insight-rx.com/>
- 829 51. NextDose. <https://www.nextdose.org/>
- 830 52. TDMx. <http://www.tdmx.eu/>
- 831 53. Kirkpatrick CM, Duffull SB, Begg EJ. 1999. Pharmacokinetics of gentamicin in 957
832 patients with varying renal function dosed once daily. *Br J Clin Pharmacol* 47:637-43
- 833 54. Neely MN, Kato L, Youn G, Kraler L, Bayard D, et al. 2018. Prospective Trial on the
834 Use of Trough Concentration versus Area under the Curve To Determine Therapeutic
835 Vancomycin Dosing. *Antimicrob Agents Chemother* 62
- 836 55. Neely M, Margol A, Fu X, van Guilder M, Bayard D, et al. 2015. Achieving target
837 voriconazole concentrations more accurately in children and adolescents. *Antimicrob*
838 *Agents Chemother* 59:3090-7
- 839 56. Woillard JB, de Winter BC, Kamar N, Marquet P, Rostaing L, Rousseau A. 2011.
840 Population pharmacokinetic model and Bayesian estimator for two tacrolimus

- 841 formulations--twice daily Prograf and once daily Advagraf. *Br J Clin Pharmacol*
842 71:391-402
- 843 57. Zhao W, Elie V, Baudouin V, Bensman A, Andre JL, et al. 2010. Population
844 pharmacokinetics and Bayesian estimator of mycophenolic acid in children with
845 idiopathic nephrotic syndrome. *Br J Clin Pharmacol* 69:358-66
- 846 58. Joerger M, von Pawel J, Kraff S, Fischer JR, Eberhardt W, et al. 2016. Open-label,
847 randomized study of individualized, pharmacokinetically (PK)-guided dosing of
848 paclitaxel combined with carboplatin or cisplatin in patients with advanced non-small-
849 cell lung cancer (NSCLC). *Ann Oncol* 27:1895-902
- 850 59. Darwich AS, Ogungbenro K, Hatley OJ, Rostami-Hodjegan A. 2017. Role of
851 pharmacokinetic modeling and simulation in precision dosing of anticancer drugs.
852 *Translational Cancer Research* 6:S1512-+
- 853 60. Wright DF, Duffull SB. 2011. Development of a bayesian forecasting method for
854 warfarin dose individualization. *Pharm Res* 28:1100-11
- 855 61. Wright DF, Duffull SB. 2013. A Bayesian dose-individualization method for
856 warfarin. *Clin Pharmacokinet* 52:59-68
- 857 62. Standing JF. 2017. Understanding and applying pharmacometric modelling and
858 simulation in clinical practice and research. *Br J Clin Pharmacol* 83:247-54
- 859 63. Keizer RJ, Ter Heine R, Frymoyer A, Lesko LJ, Mangat R, Goswami S. 2018. Model-
860 Informed Precision Dosing at the Bedside: Scientific Challenges and Opportunities.
861 *CPT Pharmacometrics Syst Pharmacol* 7:785-7
- 862 64. Administration USFaD. 2020. Proposed regulatory framework for modifications to
863 artificial intelligence/machine learning (AI/ML)-based software as a medical device
864 (SaMD): discussion paper and request for feedback. Washington DC, USA: FDA
- 865 65. Castellan AC, Tod M, Gueyffier F, Audars M, Cambriels F, et al. 2013. Quantitative
866 prediction of the impact of drug interactions and genetic polymorphisms on
867 cytochrome P450 2C9 substrate exposure. *Clin Pharmacokinet* 52:199-209
- 868 66. Lamba J, Hebert JM, Schuetz EG, Klein TE, Altman RB. 2012. PharmGKB
869 summary: very important pharmacogene information for CYP3A5. *Pharmacogenet*
870 *Genomics* 22:555-8
- 871 67. Mariappan TT, Shen H, Marathe P. 2017. Endogenous Biomarkers to Assess Drug-
872 Drug Interactions by Drug Transporters and Enzymes. *Curr Drug Metab* 18:757-68
- 873 68. Rodrigues D, Rowland A. 2019. From Endogenous Compounds as Biomarkers to
874 Plasma-Derived Nanovesicles as Liquid Biopsy; Has the Golden Age of Translational

- Pharmacokinetics-Absorption, Distribution, Metabolism, Excretion-Drug-Drug Interaction Science Finally Arrived? *Clin Pharmacol Ther* 105:1407-20
69. Diczfalusy U, Nylen H, Elander P, Bertilsson L. 2011. 4beta-Hydroxycholesterol, an endogenous marker of CYP3A4/5 activity in humans. *Br J Clin Pharmacol* 71:183-9
70. Li Y, Elashoff D, Oh M, Sinha U, St John MA, et al. 2006. Serum circulating human mRNA profiling and its utility for oral cancer detection. *J Clin Oncol* 24:1754-60
71. Patino WD, Mian OY, Kang JG, Matoba S, Bartlett LD, et al. 2005. Circulating transcriptome reveals markers of atherosclerosis. *Proc Natl Acad Sci U S A* 102:3423-8
72. Kumar S, Sinha N, Gerth KA, Rahman MA, Yallapu MM, Midde NM. 2017. Specific packaging and circulation of cytochromes P450, especially 2E1 isozyme, in human plasma exosomes and their implications in cellular communications. *Biochem Biophys Res Commun* 491:675-80
73. Conde-Vancells J, Rodriguez-Suarez E, Embade N, Gil D, Matthiesen R, et al. 2008. Characterization and comprehensive proteome profiling of exosomes secreted by hepatocytes. *J Proteome Res* 7:5157-66
74. Gotanda K, Hirota T, Saito J, Fukae M, Egashira Y, et al. 2016. Circulating intestine-derived exosomal miR-328 in plasma, a possible biomarker for estimating BCRP function in the human intestines. *Sci Rep* 6:32299
75. Console L, Scalise M, Tonazzi A, Giangregorio N, Indiveri C. 2018. Characterization of Exosomal SLC22A5 (OCTN2) carnitine transporter. *Sci Rep* 8:3758
76. Wang X, Xu C, Hua Y, Sun L, Cheng K, et al. 2016. Exosomes play an important role in the process of psoralen reverse multidrug resistance of breast cancer. *J Exp Clin Cancer Res* 35:186
77. Rostami-Hodjegan A, Achour B, Rothman JE. 2019.
78. Polasek TM, Rostami-Hodjegan A. 2020. Virtual Twins: Understanding the Data Required for Model-Informed Precision Dosing. *Clin Pharmacol Ther* 107:742-5
79. Davies EC, Green CF, Mottram DR, Rowe PH, Pirmohamed M. 2010. Emergency re-admissions to hospital due to adverse drug reactions within 1 year of the index admission. *Br J Clin Pharmacol* 70:749-55
80. Repp KL, Hayes C, 3rd, Woods TM, Allen KB, Kennedy K, Borkon MA. 2012. Drug-related problems and hospital admissions in cardiac transplant recipients. *Ann Pharmacother* 46:1299-307

81. Howard RL, Avery AJ, Slavenburg S, Royal S, Pipe G, et al. 2007. Which drugs cause preventable admissions to hospital? A systematic review. *Br J Clin Pharmacol* 63:136-47
82. Gasche Y, Daali Y, Fathi M, Chiappe A, Cottini S, et al. 2004. Codeine intoxication associated with ultrarapid CYP2D6 metabolism. *N Engl J Med* 351:2827-31
83. Eikelboom JW, Quinlan DJ, Hirsh J, Connolly SJ, Weitz JI. 2017. Laboratory Monitoring of Non-Vitamin K Antagonist Oral Anticoagulant Use in Patients With Atrial Fibrillation: A Review. *JAMA Cardiol* 2:566-74
84. Reny JL, Fontana P, Hochholzer W, Neumann FJ, Ten Berg J, et al. 2016. Vascular risk levels affect the predictive value of platelet reactivity for the occurrence of MACE in patients on clopidogrel. Systematic review and meta-analysis of individual patient data. *Thromb Haemost* 115:844-55
85. Storelli F, Samer C, Reny JL, Desmeules J, Daali Y. 2018. Complex Drug-Drug-Gene-Disease Interactions Involving Cytochromes P450: Systematic Review of Published Case Reports and Clinical Perspectives. *Clin Pharmacokinet* 57:1267-93
86. (OptimAT) ATOiHPUP-aP-bPM. <https://clinicaltrials.gov/ct2/show/NCT03477331>
87. Clarkson J, Dean J, Ward J, Komashie A, Bashford T. 2018. A systems approach to healthcare: from thinking to -practice. *Future Healthc J* 5:151-5
88. Essen A, Lindblad S. 2013. Innovation as emergence in healthcare: unpacking change from within. *Soc Sci Med* 93:203-11
89. Zhang C, Zhang C, Grandits T, Harenstam KP, Hauge JB, Meijer S. 2018. A systematic literature review of simulation models for non-technical skill training in healthcare logistics. *Adv Simul (Lond)* 3:15
90. Vinks AA, Peck RW, Neely M, Mould DR. 2020. Development and Implementation of Electronic Health Record-Integrated Model-Informed Clinical Decision Support Tools for the Precision Dosing of Drugs. *Clin Pharmacol Ther* 107:129-35
91. Neely M. 2017. Scalpels not hammers: The way forward for precision drug prescription. *Clin Pharmacol Ther* 101:368-72
92. International H. 2020. *HL7 International - Clinical Genomics Work Group*. <http://www.hl7.org/Special/committees/clingenomics/index.cfm>
93. Programme O. 2020. *Origo Programme*. <https://origoprogrammet.org/en/>
94. Murphy EV. 2014. Clinical decision support: effectiveness in improving quality processes and clinical outcomes and factors that may influence success. *Yale J Biol Med* 87:187-97

95. Roshanov PS, Fernandes N, Wilczynski JM, Hemens BJ, You JJ, et al. 2013. Features of effective computerised clinical decision support systems: meta-regression of 162 randomised trials. *BMJ* 346:f657
96. Ruano G, Robinson S, Holford T, Mehendru R, Baker S, et al. 2019. Results of the CYP-GUIDES randomized controlled trial: Total cohort and primary endpoints. *Contemp Clin Trials* 89:105910
97. Coleman JJ, van der Sijs H, Haefeli WE, Slight SP, McDowell SE, et al. 2013. On the alert: future priorities for alerts in clinical decision support for computerized physician order entry identified from a European workshop. *BMC Med Inform Decis Mak* 13:111
98. Orszag PR, Ellis P. 2007. The challenge of rising health care costs--a view from the Congressional Budget Office. *N Engl J Med* 357:1793-5
99. Nicholson S, Pauly MV, Wu AY, Murray JF, Teutsch SM, Berger ML. 2008. Getting real performance out of pay-for-performance. *Milbank Q* 86:435-57
100. Lalonde RL, Kowalski KG, Hutmacher MM, Ewy W, Nichols DJ, et al. 2007. Model-based drug development. *Clin Pharmacol Ther* 82:21-32
101. Administration USFaD. 2016. Guidance for Industry: Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products — Content and Format. Washington DC
102. Jadhav PR, Cook J, Sinha V, Zhao P, Rostami-Hodjegan A, et al. 2015. A proposal for scientific framework enabling specific population drug dosing recommendations. *J Clin Pharmacol* 55:1073-8
103. Liu T, Ghafoori P, Gobburu JV. 2017. Allometry Is a Reasonable Choice in Pediatric Drug Development. *J Clin Pharmacol* 57:469-75
104. Initiative IM. <https://www.imi.europa.eu>
105. Safety SGG-T. 2017. Newsletter. January
106. Administration USFaD. 2019. Draft Guidance for Industry: Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment Practices, and Trial Designs. Washington DC
107. Pharmaceutical spending OfEC-oaDO. <https://data.oecd.org/healthres/pharmaceutical-spending.htm>
108. Lewis PJ, Dornan T, Taylor D, Tully MP, Wass V, Ashcroft DM. 2009. Prevalence, incidence and nature of prescribing errors in hospital inpatients: a systematic review. *Drug Saf* 32:379-89

- 976 109. Roughead EE, Semple SJ, Rosenfeld E. 2016. The extent of medication errors and
977 adverse drug reactions throughout the patient journey in acute care in Australia. *Int J*
978 *Evid Based Healthc* 14:113-22
- 979 110. Harm. TtWGPSCMW. <https://www.who.int/patientsafety/medication-safety/en/>
- 980 111. Assiri GA, Shebl NA, Mahmoud MA, Aloudah N, Grant E, et al. 2018. What is the
981 epidemiology of medication errors, error-related adverse events and risk factors for
982 errors in adults managed in community care contexts? A systematic review of the
983 international literature. *BMJ Open* 8:e019101
- 984 112. Schachter M. 2009. The epidemiology of medication errors: how many, how serious?
985 *Br J Clin Pharmacol* 67:621-3
- 986 113. Singal AG, Higgins PD, Waljee AK. 2014. A primer on effectiveness and efficacy
987 trials. *Clin Transl Gastroenterol* 5:e45
- 988 114. Walley T, Haycox A. 1997. Pharmacoeconomics: basic concepts and terminology. *Br*
989 *J Clin Pharmacol* 43:343-8
- 990 115. Fischer KE, Heisser T, Stargardt T. 2016. Health benefit assessment of
991 pharmaceuticals: An international comparison of decisions from Germany, England,
992 Scotland and Australia. *Health Policy* 120:1115-22
- 993 116. Beaulieu-Jones BK, Finlayson SG, Yuan W, Altman RB, Kohane IS, et al. 2020.
994 Examining the Use of Real-World Evidence in the Regulatory Process. *Clin*
995 *Pharmacol Ther* 107:843-52
- 996 117. Gavan SP, Thompson AJ, Payne K. 2018. The economic case for precision medicine.
997 *Expert Rev Precis Med Drug Dev* 3:1-9
- 998 118. Hoebert JM, van Dijk L, Mantel-Teeuwisse AK, Leufkens HG, Laing RO. 2013.
999 National medicines policies - a review of the evolution and development processes. *J*
1000 *Pharm Policy Pract* 6:5
- 1001 119. Honig P, Lalonde R. 2010. The economics of drug development: a grim reality and a
1002 role for clinical pharmacology. *Clin Pharmacol Ther* 87:247-51
- 1003 120. Evans WE, Johnson JA. 2001. Pharmacogenomics: the inherited basis for
1004 interindividual differences in drug response. *Annu Rev Genomics Hum Genet* 2:9-39
- 1005 121. McLachlan AJ, Hilmer SN, Le Couteur DG. 2009. Variability in response to
1006 medicines in older people: phenotypic and genotypic factors. *Clin Pharmacol Ther*
1007 85:431-3

122. Yasuda SU, Zhang L, Huang SM. 2008. The role of ethnicity in variability in response to drugs: focus on clinical pharmacology studies. *Clin Pharmacol Ther* 84:417-23
123. Chenoweth MJ, Giacomini KM, Pirmohamed M, Hill SL, van Schaik RHN, et al. 2020. Global Pharmacogenomics Within Precision Medicine: Challenges and Opportunities. *Clin Pharmacol Ther* 107:57-61
124. Giacomini KM, Yee SW, Ratain MJ, Weinshilboum RM, Kamatani N, Nakamura Y. 2012. Pharmacogenomics and patient care: one size does not fit all. *Sci Transl Med* 4:153ps18
125. Norris DC. 2018. One-size-fits-all dosing in oncology wastes money, innovation and lives. *Drug Discov Today* 23:4-6
126. Marcotte LM, Schuttner L, Liao JM. 2020. Measuring low-value care: learning from the US experience measuring quality. *BMJ Qual Saf* 29:154-6
127. Elwyn G, Frosch D, Thomson R, Joseph-Williams N, Lloyd A, et al. 2012. Shared decision making: a model for clinical practice. *J Gen Intern Med* 27:1361-7
128. Hilmer SN, McLachlan AJ, Le Couteur DG. 2007. Clinical pharmacology in the geriatric patient. *Fundam Clin Pharmacol* 21:217-30
129. Hilmer SN, Gnjdic D, Abernethy DR. 2012. Pharmacoepidemiology in the postmarketing assessment of the safety and efficacy of drugs in older adults. *J Gerontol A Biol Sci Med Sci* 67:181-8
130. Rituxan. 1997.
https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/103705s5311lbl.pdf
131. Cavallo J. 2018. *Has the Promise of Precision Medicine Been Oversold?*
<https://ascopost.com/issues/october-25-2018/has-the-promise-of-precision-medicine-been-oversold/>
132. Administration USFFaD. *Prescription Drug User Fee Amendments*.
<https://www.fda.gov/industry/fda-user-fee-programs/prescription-drug-user-fee-amendments>
133. Administration USFaD. 2019. *Workshop Precision Dosing: Defining the Need and Approaches to Deliver Individualized Drug Dosing in the Real-World Setting*.
<https://www.fda.gov/drugs/precision-dosing-defining-need-and-approaches-deliver-individualized-drug-dosing-real-world-setting>

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Figure Legends

Figure 1. Example of workflow for population pharmacokinetic/pharmacodynamic (PK/PD) precision dosing. Dose personalization can be carried out either using covariates alone, to predict so called subpopulation PK, or together with therapeutic drug monitoring (TDM) and Bayesian feedback of PK or PD. Figure obtained from Wicha et al (38) with permission.

Figure 2. Workflow for model-informed precision dosing (MIPD) using the Virtual Twin framework, here exemplified with olanzapine. A priori stratification of dose to a subpopulation level can be done using patient, disease and drug data. Personalization of dose can be done using healthcare data for the individual patient. Readily available data in electronic health records (EHRs) may include: patient demographics, drug dosage regimens, clinical biomarkers, and some environmental variables. Data that is seldom available in EHRs include: pharmacogenetic information, transporter/metabolism phenotypes and abundances (via probes or liquid biopsy – see the manuscript text). Predictions can then be optimized using patient data in a ‘predict, learn and confirm’ cycle. Figure obtained from Polasek and Rostami-Hodjegan (78) with permission.

Figure 1

Figure 2