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Development and Implementation of Electronic Health Record–Integrated Model-Informed Clinical Decision Support Tools for the Precision Dosing of Drugs

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Imagine it is 2030, and the drug label is in the cloud, is interactive, and can provide model-informed precision dosing support based on an individual's genomic and physiologic makeup that is uploaded via a user-friendly interface. Precision medicine has vastly improved our ability to provide tailored therapeutics, and groundbreaking advances in noninvasive systems have generated smart wearable devices that can follow our physiologic state and drug exposure in real time. One device consists of a microfluidic drug biosensor with a transmitter attached to the skin and a mobile app that displays concentration values and trends while issuing alerts and providing suggestions on dose changes when out of range. This sounds compelling, but why has model-informed precision dosing not yet become common clinical reality in 2020?

WHY PRECISION DOSING IS NOT A CLINICAL REALITY YET

When the Precision Medicine Initiative was announced in 2015, the incentive was that medicine would become more personal with the advancement of tailor-made prevention and treatment strategies taking into account individual differences in people's genetic makeup, environmental factors, and lifestyles.[1] To date, much of the attention has gone to the targeting of specific treatments based on tumor genetics and DNA profiling in patients with cancer and diabetes.[2] Yet there is a continuing paradox in the drug development paradigm that the process is not personalized or precise, but rather population-based with the goal to identify a common dose or dose range for a particular disease that is shown to be safe and efficacious for many patients. This strategy of obtaining evidence of efficacy and safety at usual doses in populations leading to dosing guidance for the average patient complicates the precise delivery of the right dose for every patient. In addition, the drug approval process is geared toward identifying a safe and effective dose which is not necessarily an optimal dose for any individual. Yet, in many instances the dose–response and exposure–response relationships are not fully characterized or actionable despite often large between-patient variability in exposure and response.[3] This is what makes clinical decision support tools for precision dosing attractive and clinically indicated for the management of individual patients who often vary widely in their response to drug therapy.

In a recent state-of-the-art article in this journal, an expert group reported on a meeting that addressed the current status of model-informed precision dosing and why it has not yet become a common clinical reality.[4,5] Some of the inspiration came from the technological breakthroughs in the management of type 1 diabetes and its complications. In June of 2018 the US Food and Drug Administration (FDA) approved the first-ever implantable continuous glucose monitoring system.[6] This decision support system uses a glucose biosensor that is implanted subcutaneously in the upper arm and can transmit data to a cellphone. A mobile app then displays the patient's "physiologic state" by reporting glucose monitoring results in real time. Importantly, the system alerts out-of-range glucose concentrations, and the software stores, trends, and analyzes data for learning over time.[7] It highlights the fact that advanced technologies that used to be lacking (e.g., computational power, lab on a chip assays, and smart data processing) have become available. In today's world of therapeutic drug monitoring, only select drugs are assayed due in part to a lack of ubiquitous analytic capabilities and a relative paucity of evidence to definitively show improved outcomes and cost-effectiveness. While these factors hamper broad-scale adoption, the situation is rapidly changing. With advances in paper spray mass spectrometry, and biosensor, and nanotechnology, several groups are developing similar applications to continuously track drugs in bodily fluids.[8–10] We will likely soon witness the first noninvasive system to measure and transmit real-time data that facilites the precise management of drug exposure and response.[11,12]

PRECISION DOSING IN DRUG DEVELOPMENT

To achieve more precise medicine with greater individualization of dose, important changes are required in the way drugs are

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developed, approved, prescribed, and monitored.[3] During the development process, most clinical trials are designed to identify a common safe dose rather than optimizing the dosing regimen of a new drug for each individual within a target patient population. While clinical pharmacology trials focus on specific patient populations (elderly, organ impairment) and assess potential for effects of food and concomitant medications to alter drug exposure, these trials typically do not focus on other patient factors, such as genetic factors, that may alter the response to therapy. The recognition that this is an important missing element in the drug development process has been growing among drug developers, regulators, clinicians, and patients in recent years. This realization led to a full day public workshop in August of 2019 organized by the FDA in collaboration with the University of North Carolina on the topic of "Precision Dosing: Defining the Need and Approaches to Deliver Individualized Drug Dosing in the Real-World Setting."[13] Presenters identified and discussed opportunities for evidence gathering during the new drug development process including real-world data and evidence, which normally are difficult to garner during preapproval trials. However, such information may be available for approved drugs, even if approved in other countries.[14,15] One suggested framework for the development of precision dosing tools would start during early development and continue well after regulatory approval.[5,16] Sponsors should be encouraged to indicate whether their drug would benefit from precision dosing and these considerations should be included as part of the Investigational New Drug (IND) application and approval processes. In the current paradigm, valuable insights related to the level of variability in drug exposure and response are being generated but typically do not result in refinement strategies to better predict and control for this variability at the level of the individual patient. It would be highly informative if sponsors were required to provide simulations of the expected benefits in patients taking fixed doses vs. those with individualized dosing at pre–New Drug Application and ideally at end of phase II, as this would also inform phase III trial design. Alternatively, sponsors could be asked to identify what percentage of patients taking the recommended dose would be expected to have efficacy or an acceptable benefit:risk ratio and how this would look if individualized dosing were used. Increasingly exposure–response data are being used to develop informative models to help guide biomarker and pharmacokinetic/pharmacodynamic (PK/PD) assessments performed throughout early and later phase clinical trials. What is missing is easy access to this information by the end users, i.e., the clinical community. Available exposure–response data and PK/PD models should ideally be provided in the label and distributed electronically. In line with the FDA framework for a real-world evidence program, data from postmarketing surveillance registries could be further mined using modeling and machine learning approaches to refine and expand existing models and to answer questions that could not be fully addressed during the preapproval drug development process. This type of approach would not only improve the efficiency of drug development but would also have high likelihood to decrease healthcare costs while addressing a significant public health need in terms of precision medicine delivery. One of few current postapproval data/model aggregation platforms is the Drug Disease Model Resources (DDMoRe) offered by the DDMoRe Foundation, an industry–academia partnership established to maintain and enhance the pharmacometrics content delivered into the public domain by members of the European Union's Innovative Medicines Initiative DDMoRe Consortium (www.ddmore.eu).

SUGGESTIONS FOR STRATEGIES TO MOVE FORWARD

What would it take to make model-informed precision dosing common clinical practice? There are still barriers to overcome, of which one of the largest is to persuade drug developers and users that "one size fits all dosing" is no longer acceptable and that greater dose individualization, providing increased benefit and lowering risk from the drugs, is the future. To get there requires demonstrating that there is improved benefit:risk and cost-effectiveness from individualized dosing, that there is demand from patients, prescribers, providers, and payers and that the technological and regulatory barriers have been overcome. Outcomes-based pricing will be a powerful driver to wider uptake since it becomes imperative to ensure that each patient has the best chance of responding by giving a high enough dose to ensure efficacy but at the same time avoiding overtreating patients who experience adverse effects at higher doses and who would have tolerated lower doses.

The initial focus should be drugs with narrow therapeutic indices, mechanism-based adverse effects, and/or high cost. In the Netherlands, prescribers and patients responded to a decision to stop reimbursement of eculizumab for atypical hemolytic uremic syndrome by proposing individualized dosing regimens and earlier drug withdrawal based on the assessment of risk factors for relapse. The result was a more than 50% cost reduction while maintaining efficacy.[17] Renal failure care providers improved their service by the introduction of machine learning–based algorithms to improve dose individualization that both decreased costs for the provider and improved outcomes for the patients.[18] As more such postapproval cases are developed, drug developers will have increased incentives to understand dose individualization prior to approval and to pricing decisions.

POINT-OF-CARE ASSAYS

One perceived hurdle to broad dissemination of model-informed precision dosing is the relative scarcity of point-of-care assays for concentration and biomarker measurement. When biomarkers are easily available and widely understood, for example, monitoring blood glucose in diabetes, individualized dosing is the norm. Making biomarkers easily available and interpretable will be a key enabler to wider uptake, and the diagnostics industry is an important contributor to delivering this aspect of individualized dosing. In cancer drug development, companion diagnostics to identify which patients may respond best to new treatments (e.g., imatinib, trastuzumab, certuximab, vemurafenib, or anti-PD(L)1 for some indications) are gaining use because there are undoubted efficacy benefits to treating only biomarker-positive patients and the FDA streamlined the review process for diagnostics that are codeveloped with a drug.[19] Eltrombopag requires dose adjustment to achieve a target platelet concentration, and in asthma omalizumab dosing is stratified according to baseline IgE concentration, the only case of an approved drug dosed according to a marker of disease severity.

Why not adopt similar strategies for other drugs that benefit from precision dosing while also using the assays to develop informative PK/PD population models for specific target populations? It is of interest to note that the model-based approaches using Bayesian estimation pioneered in the late seventies never found a broad clinical acceptance.[20,21] This despite the appreciation, then and now, of each patient's unique PK/PD characteristics that would warrant tailoring treatment to individual needs.

One of the first prospective outcomes studies of model-based dose individualization of aminoglycoside therapy showed improved clinical outcomes at reduced cost (**Table 1**).[22] In recent years, with the advent of more powerful and user-friendly software tools, there is renewed interest in model-based therapeutic optimization and clinical pharmacometrics.[23] Neely *et al.* used modeling techniques to refute the hypothesis that vancomycin trough concentrations were an acceptable surrogate for area under the curve (AUC)[24] and then completed a prospective, AUC-guided study of nearly 300 adults showing that pharmacometrically based, individualized dosing reduced nephrotoxicity compared with trough-guided dosing, reduced associated treatment costs, and preserved therapeutic efficacy.[25] These outcomes have been replicated in an even larger study of adults with methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia.[26]

The application of such technologies to other important therapeutic areas, such as biologics to treat inflammatory bowel disease, has provided compelling case studies of its clinical impact (**Table 1**). Mould *et al.* described the evolution of Bayesian adaptive decision support software, which offer unique advantages over the earlier forms of simpler dose calculators, emphasizing benefits of improved outcomes at reduced cost.[27–30] The results of two small proof-of-concept studies (Precision Dosing of Infliximab

Table 1 Examples of case studies of model-informed therapeutic individualization and EHR-integrated clinical decision support

Drug	Indication	Goal	Details	Outcomes	References
Model-informed therapeutic optimization and clinical pharmacometrics					
Gentamicin	Gram-negative infection	Model-based target-oriented individualization	Application of Bayesian adaptive clinical software vs. standard of care	Reduced hospital stay, reduced nephrotoxicity, and reduced associated treatment costs.	Van Lent *et al.*[22]
Hydroxyurea	Sickle cell anemia	Model-informed maximum tolerated dose (MTD) individualization	Application of Bayesian adaptive clinical software to more rapid achievement of MTD	Achieved significant reduction of time to MTD and resulted in higher hemoglobin and fetal hemoglobin levels compared with traditional dosing	McGann *et al.*[39]
Infliximab	Inflammatory bowel disease	PK-guided dosing vs. standard of care	Application of Bayesian adaptive decision support software vs. standard of care	Achieved higher likelihood of maintaining remission and better disease control	Mould *et al.*[27,31]
Vancomycin	Any infection for which vancomycin was initiated	AUC-guided dosing vs. trough dosing	Pharmacometrically based, Bayesian individualized dosing	Reduced nephrotoxicity, reduced associated treatment costs, and preserved therapeutic efficacy	Neely *et al.*[24,25]
Antihemophilic factor VIII (Recombinant)	Hemophilia	Web-based application for PK-guided dosing of recombinant factor VIII	Targets factor VIII activity above a user-specified threshold to guide physicians' decisions on the frequency of dosing and appropriate dosing amount	Enables licensed healthcare professionals to provide personalized antihemophilic factor dosing schedules	Alvarez-Roman *et al.*[44]
Electronic health record–integrated clinical decision support					
Busulfan	Conditioning regimen before bone marrow transplantation	PK-guided dose individualization to reduce risk of engraftment failure or life-threatening toxicity	Optimizing the therapeutic drug monitoring process through EHR-embedded decision support tool	Provides seamless transition from patient assessment, to PK modeling and simulation, to prescription order entry and precise dose administration.	Abdel-Rahman *et al.*[38]
Methotrexate	High-dose methotrexate therapy in oncology	Individualized leucovorin rescue therapy	Model-based tracking of methotrexate clearance using EHR-linked dashboard decision support platform	Guides physicians in deciding if a patient is clearing MTX as expected or if more aggressive rescue therapy is warranted	Dombrowsky *et al.*[37]
Morphine	Pain management in neonates	Model-informed decision support for the management of neonatal pain medications	EHR-embedded model-informed dosing guidance based on pain scores and concentration feedback	Expected outcomes are better clinical efficacy and safety, fewer as-needed doses, and lower overall cumulative opioid exposure	Vinks *et al.*[47]

AUC, area under the curve; EHR, electronic health record; MTX, methotrexate; PK, pharmacokinetic.

Versus Conventional Dosing of Infliximab (NCT02453776)[31] and Precision IFX: Using a Dashboard to Individualize Infliximab Dosage (NCT02624037)) clearly indicate substantial benefits, both in terms of improved response and clinical outcomes as well as in terms of cost-effectiveness and cost savings. The first study found statistically significantly higher likelihood of maintaining remission ($P < 0.02$) with software-guided dosing than with standard of care. The second study, which is still ongoing, reported that as of last follow-up (median 49 weeks, range 9–54 weeks) 91% of patients were continuing therapy and of these patients, 95% were in steroid-free clinical remission. The study also found that optimized monotherapy using a PK dashboard is a safer alternative to combination therapy. Patients with high disease activity are especially at risk for underexposure and treatment failure. Current evidence is mounting that pharmacokinetically guided precision dosing of anti-TNF-α monoclonal antibodies does result in better disease control in inflammatory disease.[32,33]

ELECTRONIC HEALTH RECORD–INTEGRATED CLINICAL DECISION SUPPORT

The process of translating precision dosing knowledge to decision support platforms and tools that can be utilized by the medical community for patient care is not simple. Several stand-alone software packages for PK-guided dosing are commercially or freely available.[34,35] Unfortunately, most of them require manual data input and a dedicated level of training in order to become a comfortable user. This has greatly hampered broad implementation and adoption. Emerging now are electronic health record (EHR)–integrated decision support platforms that are interfaced to automatically pull patient-specific data from the system to populate a PK/PD model which generates informed options for precision dosing scenarios based on the selected target via an intuitive graphical user interface. Recent examples of EHR-integrated platforms have been described for the management of high-dose methotrexate therapy in patients with cancer[36,37] and busulfan dose optimization using a streamlined therapeutic drug management (TDM) process. The latter tool provides a seamless transition from patient assessment, to pharmacokinetic modeling and simulation, and subsequent prescription order entry and precise dose administration.[38] These reports also highlight the importance of broad stakeholder engagement and the role of clinical champions within the multidisciplinary team to successfully bring clinical pharmacometrics tools to the bedside.

So is this time different? We do have the tools to bring pharmacometrics and model-informed precision dosing directly to the bedside by integrating it into the EHR. The common approach to date has been to leave modeling tools in the hands of trained staff members who use it to give consults but reach only a minority of our patients. While we believe there will always be a role for specialists with pharmacologic training who are available for consultation on specific patients, a more promising approach is to provide all the actionable information directly to the physician and clinical teams in a comprehensible format. Creating an online resource with smartphone app capability will simplify clinical dosing, shorten time to an optimal dose, and reduce costs, all while enabling real-time and portability capabilities compared with the limited current practice as schematically outlined in **Figure 1**. This approach is being prospectively investigated for hydroxyurea therapy in patients with sickle cell anemia.[39] More quickly achieving the optimally tolerated dose will provide direct benefits of reduced time and costs and will be supplemented by indirect benefits of better health and quality of life. The novelty of the proposed platform lies in utilizing the unique capabilities of the model-informed precision dosing to provide optimized doses to affected patients living in the United States or around the world. The clinical utility of this decision tool is large, as hydroxyurea could help many thousands of children living in developing countries, where the sickle cell burden is the greatest.[40] Though this tool has been designed for hydroxyurea treatment of sickle cell disease, as a platform it will also be applicable to other diseases that use model-informed drug therapy. Companies such as Insight-Rx, DoseMe, MediWare, and Certara provide dose decision support tools that can be integrated into the EHR and provide real-time recommendations.[41] But models do not always fit the patient data well, and in those situations, evaluation by a trained provider remains essential. As with the development of

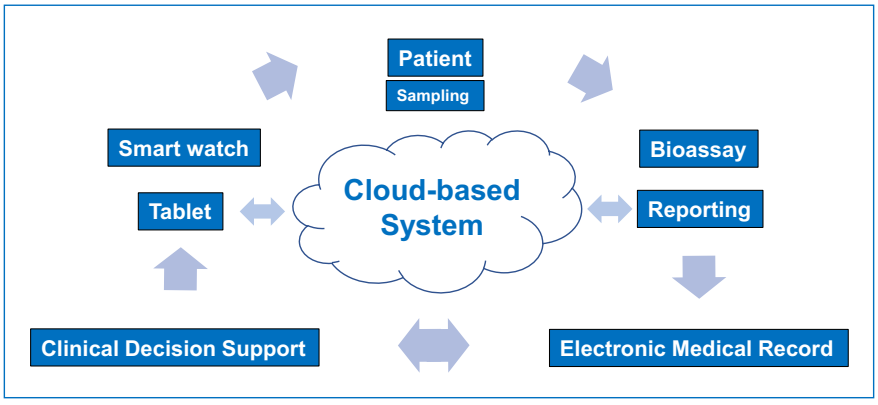

Figure 1 Schematic for an electronic health record–embedded or cloud-based model-informed decision support platform for precision dosing. The platform provides data analysis and returns clear and actionable clinical guidance to the user. This online tool has functionality for either a laptop computer platform or a smartphone device. The algorithm will receive input of timed drug concentrations, then perform Bayesian analysis using a model-informed software algorithm and generate the projected precise daily dose.

biomarkers to guide dose decisions and choices of which treatment to use, the diagnostic industry is starting to recognize the opportunity that developing such tools represents.

EDUCATION AND TRAINING

Clinical professionals will need to be comfortable accepting dose recommendations based on PK/PD and machine learning models. This is a challenge today but will be much less so in 2030 because the use of models as the engines behind many decision support tools will be much more familiar to and accepted by healthcare professionals. There will be widespread use for image analysis in radiology, pathology, and ophthalmology, for example, and it is likely that other diagnostic aids will be available using machine learning to scan all the data on a patient and identify patterns suggestive of an underlying diagnosis. However, there is need for additional emphasis on the education and training of clinical professionals, both at the pregraduate and graduate levels and those working in clinical practice to overcome cultural differences between healthcare professionals and the modeling community. Several initiatives are ongoing, including efforts by the adult and pediatric National Institutes of Health (NIH)–supported T32 clinical pharmacology training networks to disseminate know-how on modeling and simulation and pharmacometrics approaches by providing an annual webinar series and hands-on training.[42]

REGULATORY REQUIREMENTS AND CONSIDERATIONS

Software packages that provide individualized dosing recommendations are generally considered to be Class 2 medical devices and require FDA clearance to be marketed in the United States.[43] For software to be excluded from the definition of "medical device," the intended user should be able to reach the same recommendation without relying primarily on the software. Furthermore, the sources supporting recommendations and the underlying rationale for recommendation should be identified and easily accessible to the intended user, understandable by the intended user, and publicly available. This includes software that provides dose recommendations for a prescription drug that is consistent with the FDA-required labeling.

Some drugs are titrated to a pharmacokinetic (e.g., aminoglycosides) or pharmacodynamic (e.g., warfarin) target in section 2 of the prescribing information, which therefore contains the TDM information necessary for individualized dosing. For example, gentamicin contains the following recommendations: "Serum concentrations of aminoglycosides should be monitored when feasible to assure adequate levels and to avoid potentially toxic levels. When monitoring gentamicin peak concentrations, dosage should be adjusted so that prolonged levels above 12 mg/L are avoided. When monitoring gentamicin trough concentrations, dosage should be adjusted so that levels above 2 mg/L are avoided." Bayesian adaptive dosing systems for titrated drugs may be consistent with the FDA-required labeling because the dosing recommendations that these systems provide are consistent with section 2. However, as the label indicates that dose adjustments should be based on measured peak and/or trough concentrations, use of a Bayesian dosing algorithm to customize the initial dose, prior to measuring concentrations based only upon relevant patient factors included in the model (e.g., creatinine clearance), is inconsistent with the label.

Thus, the regulatory path of any software device depends upon the type of information contained in section 2 of the respective drug labeling. If TDM is present in section 2, and dose adjustments based on TDM results are described, the software may be cleared as long as the dose recommendations are completely aligned with the labeling. For software that is intended to be used with drugs that contain only population dosing in section 2 of the prescribing information (which may include dose adjustments for varying conditions, such as renal impairment), with limited ability to adjust the amount or timing of dosing, the issue of "outstanding drug issues" has been used to prohibit clearance of devices, and thus, FDA clearance is not currently possible. At present, only one Bayesian adaptive dosing software system has been cleared by the FDA (BK170028 "MyPKFit"), and this system, which adjusts the dose of factor VIII, is consistent with the prescribing information.[44]

For devices that are cleared by the FDA (or are excluded from the definition of "device") but are incorporated into EHRs or link to these systems, the software also requires testing and certification from Health IT. Such certification ensures that the software communicates with the EHR system and correctly retrieves or identifies appropriate information for use.

INDIVIDUALIZED FORMULATIONS

Today, individualized dosing is realistic for parenteral drugs and those with liquid formulations but can be challenging for drugs only available as solid dosage forms. Different strengths may exist, for example, for use in patients with organ failure or taking interacting concomitant medications, but even then choice of dose is limited. However, this is another problem that we will likely have been solved in 2030. Three-dimensional bioprinting is being developed as a means to produce combination pills where the precise combination of drugs can be individualized for each patient.[45,46] Such systems can enable individualized dosing, too. In 2030, or soon after, there will be a return to the compounding role that used to be an essential part of pharmacy practice.

CONCLUDING REMARKS

This time, things are different. Important progress has been made with several precision dosing software tools now operational in EHR systems. In addition, several proof of concept studies have shown feasibility and positive impact on patient outcomes. However, there is more work to be done, starting with the development of clearly defined pathways for Health IT certification and regulatory clearance. To date, only one Bayesian system has been cleared in the United States. The FDA clearance of myPKFit (Takeda Pharmaceutical Company Limited, Lexington, MA) represents an important milestone for the precision dosing of factor VIII in the management of hemophilia. It is unclear at this point what the regulatory pathway for clearance for precision dosing software would look like if the software is more generic and capable of generating model-informed recommendations for different drugs and indications that are not aligned with the current label. Some of these topics were discussed at the FDA workshop on precision dosing, but it was noted that important

pieces are already in place. In terms of stakeholder incentives, outcomes-based pricing will drive this if the technology can help avoid nonresponse because of inadequate dosing or nonresponse because of poor adherence when the patient stops the drug because of adverse effects. Diagnostic companies could be attractive partners in this respect as they increasingly recognize an opportunity to develop and market clinical decision support tools. In conclusion, there are regulatory barriers, but the diagnostics industry recognizes an opportunity, and these developments may have a positive effect on the pharma industry by reversing what has mostly been recognized as a problem to avoid, as opposed to a precision-medicine and patient-centered opportunity.

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CONFLICT OF INTEREST

A.A.V. declared no competing interests for this work. R.W.P. is an employee and stockholder of F. Hoffmann la Roche. M.N. developed precision dosing software currently licensed to InsightRX. D.R.M. is president of Projections Research Inc., a company that provides consulting services to the pharmaceutical industry. As Associate Editors for *Clinical Pharmacology & Therapeutics*, A.A.V. and R.W.P. were not involved in the review or decision process for this paper.

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