PERSPECTIVE

# Perspectives on Model-Informed Precision Dosing in the Digital Health Era: Challenges, Opportunities, and Recommendations

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**Drug approval is based on exposure, response, and variability of studied populations, typically excluding comorbidities/medications and very ill patients, thus not representing real-world populations. This results in wide variability in therapeutic outcome for *individual* patients. Model-informed precision dosing (MIPD) can characterize/quantify this variability, support optimal dose selection, and enable individualized therapy. The aim of this perspective is to raise awareness for MIPD, identify challenges hindering its implementation in clinical practice, provide recommendations, and highlight opportunities.**

MIPD aims at tailoring doses to patients' needs, and therefore presents a promising tool to increase treatment success.[1] Within a Bayesian framework, typically prior knowledge about drug pharmacokinetics (PK) and exposure-response relationships are individualized based on individual patient characteristics ("covariates," e.g., age, weight, sex, disease characteristics, or comedication) and PK or biomarker data to obtain individual model parameters (maximum a-*posteriori* estimates). Recently, Bayesian data assimilation methods have come into focus, overcoming major limitations of maximum *a posteriori*-based approaches by enabling accurate uncertainty quantification and propagation.[2] In contrast to traditional and well-established therapeutic drug/biomarker monitoring (TDM), MIPD provides quantitative decision support to healthcare professionals for real-world patient populations integrating multi-level data. With the increase in available computing power,[3] further methodological advances enabling a comprehensive uncertainty quantification,[2] numerous publications demonstrating the clinical benefits of MIPD,[4] and also the user-friendliness of few already existing MIPD tools,[5] the question arises as to why the implementation of MIPD in clinical practice—with the exception of local initiatives at academic hospital centers[6]—still largely fails. In the following, we summarize selected key challenges that need to be addressed, and further perspectives beyond (see also **Figure 1**, **Table 1**). We propose an alignment for terminology and across scientific disciplines, thus enabling collaborative work. Furthermore, we provide a comprehensive literature overview of current applications, review articles, innovative methodology, initiatives, and already available software tools (**Table S1**).

## DEFINITION/TERMINOLOGY

MIPD is a rapidly evolving research area in which multiple scientific disciplines/communities and other stakeholders meet. Due to the diverse origins of MIPD research projects or MIPD tools, various terms exist in the literature for these approaches and methodologies (**Table 1**). As a result, terms and labels are used interchangeably, and although there are many common features, various MIPD initiatives exist in parallel without touch points. Harmonization of the definitions across different therapeutic areas and scientific disciplines is therefore crucial.[7] Following the successful example of "model-informed drug discovery and development" a joint effort and unified appearance under the consensus term "MIPD" will ensure greater visibility

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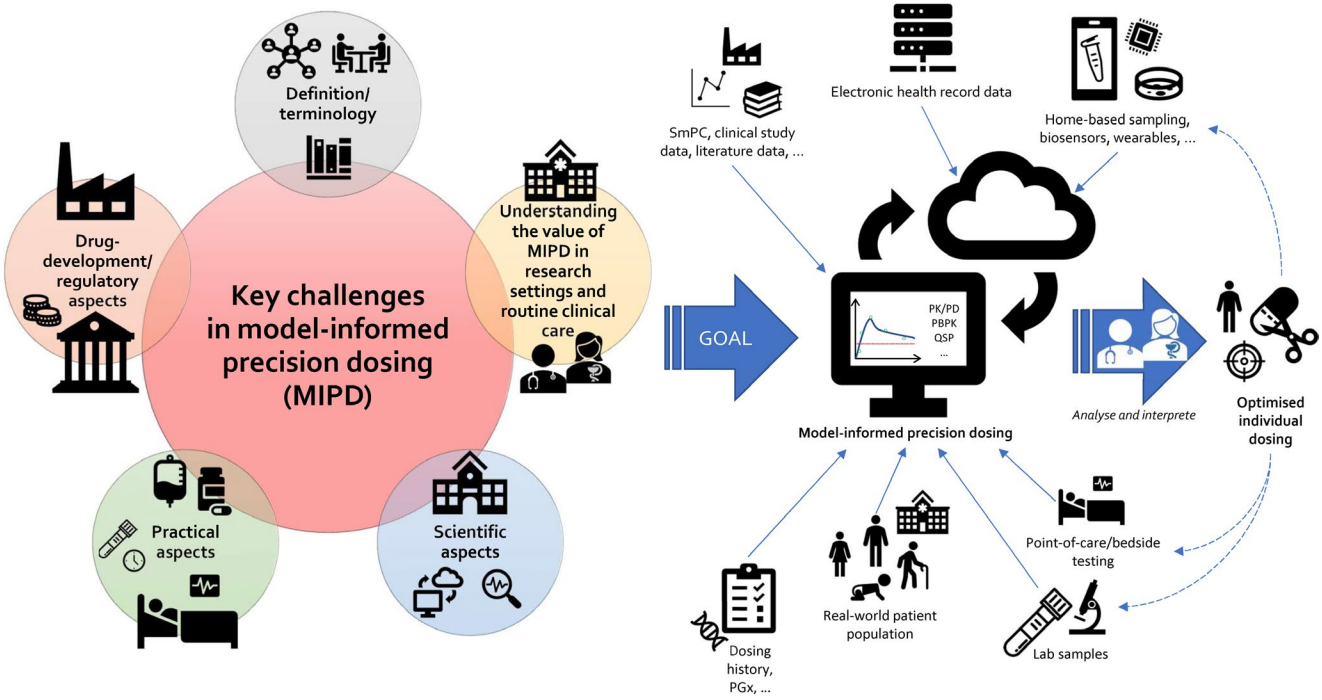


**Figure 1** Key challenges and perspectives for model-informed precision dosing (MIPD). PBPK, physiologically-based pharmacokinetics; PD, pharmacodynamics; PGx, pharmacogenomics; PK, pharmacokinetics; QSP, quantitative systems pharmacology; SmPC, summary of product characteristics.

and extension of the target audience to facilitate and accelerate implementation of MIPD in drug development and clinical practice. Complementary to this, MIPD must be recognized as a collaborative effort between different scientific disciplines, which ought to be leveraged in research projects investigating and developing MIPD approaches/tools. Only through collaborative efforts, MIPD can be realized and will become a clinical reality. Moreover, the term "precision medicine" also comprises other approaches (e.g., pharmacogenomics), which are often seen as unconnected with MIPD, at times even competing concepts in scientific discourse and clinical practice, whereas they should rather be understood as complementary approaches to take full advantage of them. MIPD offers the potential to serve as a platform simultaneously integrating various approaches for therapy individualization and optimization.[4]

## UNDERSTANDING THE VALUE OF MIPD IN RESEARCH SETTINGS AND ROUTINE CLINICAL CARE

A major obstacle is still constituted by the fact that current curricula for physicians, clinical pharmacists, and other healthcare professionals are lacking in-depth training in quantitative pharmacology, which is needed to enable understanding, application, and evaluation of MIPD concepts and tools. This needs to be addressed via increasing awareness (e.g., by publishing good examples and "best practices" in the right journals,[7] and presenting at conferences and workshops) and education (offer more training opportunities to acquire knowledge and expertise in model-informed/quantitative approaches). User-friendly software and integration into clinical workflow are ultimately needed to remove the remaining barriers and unleash the full power of MIPD tools. Healthcare professionals involved in drug treatment need to understand that "one-dose-fits-all" must be replaced by MIPD for the individual patient to improve therapy outcome. An MIPD tool will offer decision support, but the decision about the individual therapy still rests with the treating physician or clinical pharmacist, who integrates the overall status of the patients. Additionally, current regulatory (e.g., registration of MIPD tools as medical devices) and healthcare system (e.g., reimbursement framework) level barriers further discourage the application of MIPD in clinical routine. Joint efforts among the scientific community promoting MIPD, healthcare professionals, pharmaceutical companies, and stakeholders in the regulatory/healthcare system environment are required.

## SCIENTIFIC ASPECTS

MIPD provides opportunities for various approved and investigational drugs, however, not all drug therapies might benefit. Drugs with high associated treatment costs, potential severe adverse drug reactions or a narrow therapeutic index, and/or associated high interindividual variability, are particularly qualified for precision dosing. However, there must be a reliable correlation between the drug or surrogate biomarker concentration (preferably in a readily available matrix) and the clinical effect. In addition, robust therapeutic PK, pharmacodynamic, or PK/pharmacodynamic targets, utility functions, or target ranges must be established and thoroughly evaluated, which warrant large-scale clinical trials and observational studies in "real-world" populations, if not yet established during drug development. This can be particularly challenging for drugs with delayed (un-)desired effect (e.g., chemotherapy), for which drug tolerance is

**Table 1 Challenges, opportunities/recommendations, and future perspectives identified in MIPD**

| Aspect | Challenges | Opportunities/recommendations | Future perspectives |
|---|---|---|---|
| *#1 Definition and terminology* | | | |
| Definition | Various terms exist in the literature and are often used interchangeably (e.g., TDM, feedback-controlled TDM, proactive TDM, proactive dose adjustment, target concentration intervention, precision dosing, MIPD, Bayesian forecasting, Bayesian feedback, Bayesian dashboard, optimal/adaptive control, optimal/adaptive feedback, clinical decision support etc.) | Harmonization of the definitions across different therapeutic areas and scientific disciplines to emphasize and strengthen the common (similar) character; join forces to overall gain more visibility | Joint efforts can extend the target audience and facilitate and accelerate implementation of MIPD in drug development and clinical practice/therapeutic use |
| MIPD is a collaborative effort between different scientific disciplines and multiple stakeholders | Different scientific disciplines (e.g., clinical pharmacology, clinical pharmacy, laboratory medicine/chemistry, pharmacometrics, (bio-)informatics, (bio-)statistics, physics, mathematics, systems biology/pharmacology) need to be joined in research projects investigating MIPD and furthermore need to collaborate with other stakeholders in the regulatory environment and healthcare system to implement MIPD in clinical practice | Strengthen collaborations and bring loose ends together to enable implementation of MIPD | Only through collaborative effort, MIPD can be realized and will become clinical reality |
| *#2 Understanding the value of MIPD in research settings and routine clinical care* | | | |
| (Un)known value of MIPD | Physicians and clinical pharmacologist (often) do not know the value that MIPD could bring to their routine clinical care and therefore do not have interest in this approach | Improve overall quality of life for patients, through optimized dosing and thus individualized care, which improves patient outcome by minimizing toxicity and maximizing therapeutic outcome | Precision dosing can occur at the start of therapy once risk groups and appropriate doses are identified with MIPD and machine learning |
| Training of physicians and clinical pharmacists | Current curricula are lacking in-depth training in model-informed approaches, that would be needed to understand, use and evaluate MIPD concepts and tools | Gaining knowledge and expertise in model-informed approaches | More training opportunities, user-friendly software and integration in clinical workflow will lower barriers to leverage the power of MIPD tools |
| Legal framework | Regulatory and healthcare system level barriers including reimbursement frameworks discourage use of MIPD | Stakeholders in regulatory agencies and healthcare systems are open for input and discourse | The future of MIPD will be shaped now through joint initiatives and multi-stakeholder discussions |
| | Accountability and responsibility for development of MIPD tools (e.g., registration as medical device) and correct use and interpretation (physician, modeler, patient, pharmaceutical company) | | |
| Software licenses | Licenses are expensive, but needed for reimbursement of development and ensuring quality and future developments of software | Research- and education-driven free platforms can co-exist with commercial systems | Research- and education-driven free platforms are valuable for training and teaching, more commercial tools and tools developed by pharmaceutical industry will emerge |

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**Table 1 (Continued)**

| Aspect | Challenges | Opportunities/recommendations | Future perspectives |
|---|---|---|---|
| Reimbursement framework | The development, validation and maintenance of software tools, the acquisition of licenses, the training of personnel, the additional workload entailed, or the performance of additional studies are not compensated for by the health-care system | Reimbursement of remote MIPD services without face-to-face patient encounter includes savings potential compared with the current practices and poor outcomes<br>Especially exchange, partnering and learning from business development units at academic research centers can foster the promotion and development of business models for MIPD tools (e.g., "Research to Market Challenge" at FU/HU/TU/Charité Berlin) | Poor outcomes from drug therapy and drug-related harm represent a significant financial cost to healthcare systems that can be prevented |
| Cost-benefit analyses | Large scale cost-benefit analyses are lacking to demonstrate financial advantages through implementation of MIPD | Continuous learning through machine learning capabilities, clinical/operational metrics and link to outcomes can show cost benefit | Saving money by improving patient outcomes is possible |
| *#3 Scientific aspects* | | | |
| Suitability of a drug for precision dosing | Not all drugs are suitable for MIPD (particularly qualified: drugs with high associated treatment costs, potential severe adverse drug reactions or a narrow therapeutic index and/or associated high interindividual variability) | More advanced therapy options and increasing complexity of treatment decision making will occur in the future | Having MIPD tools at hand and integrated in clinical environment will facilitate future challenges with expected increasing complexity of drug treatment and patients having multiple comorbidities |
| Available PK, PD, PK/PD targets, or (surrogate) biomarkers | Especially for "old" drugs, PK, PD, PK/PD or biomarker targets are lacking, relationship between biomarker and long-term therapeutic outcome must be established, cost-effective and minimal invasive measurement of the biomarker is essential | Evaluate experimental targets through MIPD and simultaneously integrate knowledge on multiple end points (e.g., for efficacy and toxicity)<br>Once drugs are available as generics, there should be a funding system enabling MIPD studies, which is equipped by the reimbursement bodies and all drug companies selling this special drug | MIPD will contribute to establishing new, and if needed, challenging old and new targets |
| Underlying methodology for MIPD | More and more emerging methodologies and ongoing debate about which M&S approach is most suited for which type of data analysis or clinical application | It is important to progress beyond the debate of which M&S approach is "best" or most appropriate, and explore their complementarity for MIPD; ideally create guidelines and recommendations that can assist with this challenge | Joint complementary approaches should be aligned where possible to facilitate training and implementation |
| Underlying model for MIPD | Several models might be available for the same drug in terms of structural model, but also on the level of model parameter estimates, significant covariates and residual variability models; models are often only validated on the same data which was used to develop the model (independent training and test data sets would be needed) | Integrate information from different models (meta-analysis) or use model averaging | Pooling of available data and continuous updating with new incoming data allows the best assessment of the "best" model |
| Building up trust in MIPD | For a given MIPD approach, it would be desirable to clearly communicate, which data were used for development (training data) and which data were used for validation (test data), including the design of the corresponding studies (patient characteristics, numbers etc.) | A platform of exchange for each MIPD tool would be desirable: report about where this tool is already in use, for how long, with which experiences, collect credentials (quotes from healthcare providers using the MIPD tool), illustrate the predictive power and evaluate on a regular basis the performance of the tool, exchange parameter distributions for special populations etc. | Examples for such platforms in other areas already exit and can serve as blueprint (e.g., DDMoRe for MID3, http://www.ddmore.eu/) |

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**Table 1 (Continued)**

| Aspect | Challenges | Opportunities/recommendations | Future perspectives |
|---|---|---|---|
| Translation of academic research into easy-to-use software tools for clinical practice | Translation of findings into easy-to-use software tools is a crucial and challenging part of MIPD implementation, expertise beyond pharmacology and pharmacometrics is needed | Several easy-to-use tools are already available and evaluated, their features should serve as a blueprint for further developments<br>Implementation strategies need to be evaluated, i.e. what works best for educational purposes and communication of MIPD tools | Following successful examples for MIPD tools and other healthcare applications, guidelines and best-practices should be established |
| Evaluation/validation of tools | Thorough training and evaluation/validation is difficult to set up; evaluation of tools rare and scientific consensus on how not available | Shaping the direction of required/desired training, evaluation/validation is possible through open discourse within the scientific community | With growth of the user community, training offers, and publications regarding evaluation/validation of MIPD tools will expand |
| Prospective proof-of-concept studies investigating benefits of MIPD in comparison to flat dosing | Until now, larger trials investigating benefits of MIPD are lacking for approved drugs, as well as NDA/BLA | Prospective studies are key determinants for the uptake of MIPD and its reimbursement<br>Collecting/analyzing data and learning through MIPD tools facilitates their own large-scale evaluation | Results from larger trials (e.g., AutoKinetics trial), will be available and show benefits of MIPD, contribute to establishing guidelines for consideration of MIPD during drug development, and facilitate reimbursement |
| Guidelines | Lack of guidelines how to implement und successfully realize MIPD for specific drugs and diseases | Collaboration between PMx community and societies of special disease areas | PMx will be globally applied in developing treatment postapproval guidelines |
| PGx | PGx and MIPD concepts exist in parallel without touch points | PGx and MIPD are complementary approaches | Combining available knowledge on PGx and MIPD, therapy individualization will be enhanced |
| New approaches (e.g., big data, machine learning, sensors, and wearables) | Promising new approaches, however, integration of model-informed and data-driven approaches critical | Build partnerships with experts in these fields | Research collaborations will enable integration of big data and machine learning modules in MIPD tools, making them "smart" tools updating their own proposed sampling or dosing algorithms |
| *#4 Practical aspects* | | | |
| Infrastructure | Integration of available patient data difficult and time-consuming (paper records, reporting of bioanalytical results) and connection between home monitoring devices or wearables to the hospital/physician lacking | As EHR systems and bedside analytics become widely available, integration and interfaces with MIPD tools should be expanded | With technical progress, this should soon no longer pose a challenge (caveat: low-income countries) |
| Sharing of patient data | Sharing of sensitive patient data across hospitals and study centers might pose challenges | Models are tools which can be shared across clinics | Discussions on how and to which extent patient data can be shared are warranted and experience can be gained through other fields of digitalization |
| Timing, quality, and quantity of PK/biomarker samples | Can be resource limited (e.g., when, how often to sample, where/by whom to sample, i.e. at the clinic or at home) | Implement optimal design modules/approaches in MIPD tools, in addition MIPD is more flexible regarding sampling timepoints compared to traditional TDM (but only if the actual time is correctly stated) | Using model-informed approaches and tools, optimal design will become a tandem discipline to facilitate and reduce sampling |
| Bioanalytical turnaround time of samples | Often several hours to weeks until information is available for MIPD | Raise awareness for benefits of optimal (often less) sampling timepoints, shorter turnaround times and streamline internal processes; introduce new concepts (e.g., bedside/point-of-care analytics and diagnostics, or sensors and wearables) | Understanding MIPD as team effort integrating efforts from different department and disciplines, as well as newly available technology (biosensors) will drastically reduce turnaround times |

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**Table 1 (Continued)**

| Aspect | Challenges | Opportunities/recommendations | Future perspectives |
|---|---|---|---|
| Individualization of dosage form | Realization of individual dose difficult due to available pharmaceutical dose forms (dosage form) | With a greater available dose range, higher response rates and fewer adverse drug reactions are possible | Dose individualization will be considered more during drug development and new technology like 3D printing will further enhance possibilities to produce custom medication formulations |
| | Product labelling lacking titration information | More room for considerations of MIPD in drug development | |
| *#5 Drug-development/regulatory aspects* | | | |
| MIPD as part of MID3 during drug development | MIPD/special patient populations often not considered during drug development until NDA (phase III studies) | Following the examples of prospective proof-of-concept studies evaluating MIPD for approved drugs, clinical trials investigating MIPD for NDA/BLA (if indicated) could be integrated in the drug development process as part of MID3<br>Improving our understanding of the underlying causes of variability in patient response should catalyze an increase in the numbers of drugs that are shown to be safe and effective and make it to the market | Labels will include more precision dosing recommendations for different patient populations and validated MIPD software tools will be made available during drug development |
| Development/ regulatory path for MIPD tools | Development/regulatory path (often) remains unclear to pharmaceutical companies | Initialize meetings and workshops on behalf of regulatory agencies to jointly shape the future direction of regulatory guidances integrating learnings from proof-of-concept studies evaluating MIPD for approved drugs, establishing links to an attractive reimbursement framework | More joint initiatives involving pharmaceutical industry, clinical practitioners, academia, and regulatory agencies will be kicked-of |

BLA, biologic license application; DDMoRe, Drug Disease Model Resource; EHR, electronic healthcare records; M&S, modelling and simulation; MID3, model-informed drug discovery and development; MIPD, model-informed precision dosing; NDA, new drug application; PD, pharmacodynamics; PGx, pharmacogenomics; PK, pharmacokinetics; PMx, pharmacometrics; TDM, therapeutic drug monitoring.

often developed (e.g., depression) or active metabolites. Next, if a drug is identified as a suitable candidate for MIPD, there is often more than one model or methodology applicable. Pooling of available data (or even models) for the same drug-disease system and continuous updating with new incoming data allows to capture most realistic patient population scenarios into a single model most appropriate for use in MIPD. In the future, as more frequent sampling (biosensors, wearables, point-of-care, or home-sampling devices) and advanced data-analysis methods (e.g., data assimilation or machine learning), become available for MIPD, better informed and automated precision dosing could be achieved. Nevertheless, also in the future using big data and machine learning, the quality of the available data and the mechanistic understanding of the underlying processes are crucial. Despite readily developed MIPD tools emerging from academic/clinical research collaborations, implementation into routine clinical care often fails. Translation of research findings into easy-to-use software tools is a crucial and challenging part of MIPD implementation, and expertise beyond quantitative pharmacology/pharmacometrics is needed. Implementation research is required: there are various implementation strategies (training, education, adaptability, flexibility, and changed clinician behavior) that need to be explored and evaluated to increase the uptake of MIPD into routine clinical practice. Following successful examples for MIPD tools[5] (and also other healthcare applications, **Table S1**), the establishment of guidelines and "best practices" should be fostered. Furthermore, in collaboration with medical societies, guidelines how to implement and successfully realize MIPD for specific drug-disease systems should be established, as they are currently still lacking. Next to disease areas in which traditional TDM is well-established (e.g., infectious diseases, immunology, or transplantation medicine), new fields of application can be identified for MIPD.

## PRACTICAL ASPECTS

Besides scientific questions, there are many practical challenges that need to be addressed for implementation of MIPD in patients' drug therapy. First, the clinical infrastructure needs to be adapted to be ready for MIPD use at the bedside, but also for providing optimal ambulant or home-based therapies using digital healthcare devices (e.g., wearable biosensors or point-of-care devices) that allow patients to measure and report online individual drug/biomarker concentrations. In the hospital, integration of available patient data might be difficult and time-consuming if they are still paper-based or multiple software tools are used for analysis, reporting, and communication of clinical samples. As electronic health record systems and point-of-care devices become widely available, integration and interfaces with MIPD tools should be explored and expanded to further support and accelerate this digital trend. With today's technical progress, this should soon no longer pose a challenge at least for high-income countries with good healthcare systems. Implementation of model-informed and optimal design approaches can further contribute to overcome "classical" TDM problems, such as inappropriate timing, quality, and quantity of PK or biomarker samples. Often highlighted major concerns in traditional TDM still comprise long bioanalytical turnaround times of samples (several hours to weeks), lack of standardization in workflows, and high instrumentation costs with complex sample preparation.[8] Raising awareness for benefits of optimal (often earlier and less) sampling timepoints, streamlining internal processes to shorten turnaround times, and introducing new concepts (e.g., point-of-care/bedside analytics, biosensors/wearables, and home-monitoring systems[9]), using not only plasma, but also, for example, saliva, interstitial fluid, or capillary blood, will offer practical solutions to the challenges listed above.

## DRUG-DEVELOPMENT/REGULATORY ASPECTS

Nowadays, pharmacometric approaches are widely used within drug research and development and model-informed approaches (MID3) have been well accepted by regulatory agencies. Therefore, further exploiting their potential in postapproval phases, particularly to investigate populations that have not been well-studied within clinical development (e.g., pregnant women and obese patients) should be encouraged. For future drug development, it should be acknowledged that accepting more complex dosing will trigger higher response rates and fewer adverse drug reactions, thus facilitating drug approval and reimbursement.[10] Recently, regulatory agencies and stakeholders in the healthcare systems have increasingly acknowledged the value and opportunities of MIPD and are open for input and discourse. The regulatory and reimbursement frameworks will need to adapt to, but at the same time also trigger changing trial designs, methods of analysis, and more flexible and complex dosing recommendations. Of course, this does not apply for all investigational new drugs, but the right candidates should be identified early (e.g., based on projected low therapeutic indices or high treatment costs), and incorporation of precision dosing should become a key consideration for approval, reimbursement, or therapeutic use.[10] First initiatives with regard to precision dosing were kicked-off by regulatory agencies[11] and the potential of MIPD should also be evaluated for other existing initiatives, such as the development of so-called "companion diagnostics."

## CONCLUSIONS

Global awareness of the emerging need for precision dosing instead of the historic "one-dose-fits-all-approach" for established but also newly approved and investigational drugs is rising. New mobile healthcare devices gathering data from various sources become available, and the overall complexity of treatment decision making increases. Keeping pace in the era of digital health is only possible through advances in the field of MIPD. This includes user-friendly, evaluated, and scalable decision-support tools integrated in the clinical workflow, improved training for physicians and clinical pharmacists, establishment of "MIPD good practices," and eventually initiatives investigating the benefits of such MIPD tools over current practices. For the future of MIPD, we envision that MIPD will not only become an integral part of drug development, intrinsically motivated by initiatives within pharmaceutical companies, and as a requirement by regulatory agencies, but also that through

education, training, and widespread availability, its application goes beyond academic hospital centers in high-income countries and becomes readily available for more patients in need for optimized and individualized therapy. Multistakeholder collaborations ranging from drug development to real-world and bedside application will be crucial to validate, implement, and demonstrate the value of MIPD.[11]

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