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Artificial Intelligence Opportunities to Guide Precision Dosing Strategies

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ABBREVIATIONS AI, artificial intelligence; EHR, electronic health records; HITECH, Health Information Technology and Reinvestment Act; MIPD, model-informed precision dosing; ML, machine learning; PMAP, precision medicine analytics platform; PD, pharmacodynamics; PK, pharmacokinetics; TDM, therapeutic drug monitoring;

KEYWORDS AI; EHR; individualized pharmacotherapy; MIPD; precision dosing; RWD; RWE

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Precision Dosing: History and Current Status

Precision dosing is an approach to use various patient-specific data sources to individualize pharmacotherapy of critical medicines used in the care of disease and other conditions for which drug therapy is recommended. Often the "data" in question refers to therapeutic drug monitoring of drug concentrations in blood or plasma. More recently, biomarkers and clinical outcomes have been used to further guide dose individualization for critical pharmacotherapy. The first model-informed precision dosing (MIPD) tool using both pharmacokinetics (PK) and pharmacodynamics (PD) data was developed in 1969, to assess optimal dosing for patients on anticoagulation therapy.[1] The concept has matured in the decades since then, with many proposing various methodologies and solutions. Many have contributed to the discipline, and much of the field owes a debt of gratitude to Roger Jelliffe,[2] who pioneered the discipline in many ways, contributing scientific rationale, therapeutic drug monitoring (TDM) modernization, bioanalytic requirements, sophisticated models, and algorithms and tools as well as clinical evaluation and implementation.[3,4] During the past several decades, technologic advances, such as the ubiquity of electronic health records (EHRs), increased data accessibility, and the emergence of cloud-based infrastructure, have enabled the adoption of MIPD at scale. Despite the technologic improvements and advances there are still limited implementations of either internal or commercial solutions, and the limited implementations typically are for single institutions and not collaborative efforts where data and/or models and decision support systems are shared.

Precision medicine takes into account individual differences in patients' genes, environments, and lifestyles seeking to maximize the quality of health care by individualizing the process to the uniquely evolving health status of each patient. The approach spans a broad range of scientific areas, including drug discovery, genetics/genomics, health communication, and causal inference, all in support of evidence-based, that is, data-driven, decision-making.[5] Precision medicine is formalized as a treatment regime that comprises a sequence of decision rules, one per decision point, which map up-to-date patient information to a recommended action. The potential actions could be the selection of which drug to use, the selection of dose, timing of administration, specific diet or exercise recommendation, or other aspects of treatment or care.[6] Given the scope of precision medicine, synergy with precision dosing initiatives is obvious, especially from the standpoint of data requirements and the need for a sophisticated platform that integrates diverse data sources and provides analytics capabilities. Both commercial and homegrown (academic) platform solutions exist for precision dosing, but these are seldom integrated into a larger precision medicine platform solution.

AI Utilization in the Care of Patients

Artificial intelligence (AI) has evolved into a powerful tool that uses varied knowledge stores and provides rapid solutions to complex problems. Advancements in AI technology and machine learning have provided a transformative opportunity in the drug discovery, formulation, and testing of pharmaceutical dosage forms. By using AI algorithms that analyze extensive biologic data, including genomics and proteomics, researchers are able to identify disease-associated targets and predict their interactions with potential drug and vaccine candidates.

The power of AI technologies to recognize sophisticated patterns and hidden structures has enabled many image-based detection and diagnostic systems

in health care to perform as well as or better than clinicians, in some cases. AI-enabled clinical decision-support systems may reduce diagnostic errors, augment intelligence to support decision-making, and assist clinicians with EHR data extraction and documentation tasks.[7] Emerging computational improvements in natural language processing, pattern identification, efficient search, prediction, and bias-free reasoning will lead to further capabilities in AI that address currently intractable problems.

Advances in the computational capability of AI have prompted concerns that AI technologies will eventually replace clinicians. The term "augmented intelligence," first used by W.R. Ashby in the 1950s,[8,9] may be a more appropriate description of the future interaction between data, computation, and health care providers and likely provides a better definition for the abbreviation "AI" in health care, as others have pointed out.[10,11] Augmenting human decision-making with guidance provided by AI leads to actionable insights in numerous clinical arenas, such as oncology, imaging, and primary care. Many examples exist. A breast cancer predicting algorithm, trained on 38,444 mammogram images from 9611 women, was the first to combine imaging and EHR data with associated health records.[7] This algorithm was able to predict biopsy malignancy and differentiate between normal and abnormal screening results and can be applied to assess breast cancer at a level comparable to that of radiologists, as well as having the potential to substantially reduce missed diagnoses of breast cancer. Combined machine-learning and deep-learning models trained on a data set of linked mammograms and health records may assist radiologists in the detection of breast cancer as a second reader.

More recently, Deep Patient, an AI tool used at Mount Sinai Hospital in New York to review the medical records for approximately 700,000 patients, was able to predict a wide range of diseases in the patients without any instructions provided by experts.[12] This included anticipating the onset of psychiatric ailments, such as schizophrenia, in some patients. However, Deep Patient has limitations with no way of providing the rationale on why those patients were identified. One interesting example that has gone beyond the proof-of-concept stage is the precision medicine platform developed at Johns Hopkins. The Johns Hopkins University Applied Physics Laboratory and Johns Hopkins Medicine, in partnership with the Bloomberg School of Public Health, Johns Hopkins Information Technology, and others across the institution, have jointly developed the precision medicine analytics platform. This platform pulls data from many sources, aggregates the data, and then provisions needed data to approved researchers in a secure environment where they can apply advanced techniques and other tools to analyze the data. The guiding vision is to create and sustain the ability to accelerate gaining knowledge and value from data and from closing the loop between discovery and delivery, ultimately reducing health care costs and improving patient outcomes.[13]

The emphasis of personalized medicine is placed on tailored prevention, diagnosis, and treatment for each individual based on individual genetics, phenotype, epigenetics, and lifestyle. There continues to be a belief by some that deep phenotyping of every individual is necessary before precision medicine interventions can be applied.[14] More recently, AI and ML algorithms have been shown to be modernizing several aspects of patients' lives through their implementation in precision medicine strategies, including medical imaging, risk analysis, phenotype prediction, and analysis of gene expression patterns. Table 1 provides some examples of AI integration into various precision medicine practices along with their current or potential effects.

Both precision medicine and AI techniques affect the goal of personalizing care in 5 ways: therapy planning using clinical, genomic, or social and behavioral determinants of health, and risk prediction/diagnosis, using genomic or other variables.[7] Validating these conceptual ideas remains a work in progress for many of these theoretical gains, as does the development of tools that facilitate routine implementation.

AI as a Complement to Precision Dosing Strategies

Because individualized pharmacotherapy is agnostic to both tools and methodologies, there is an opportunity to expand the horizon of current MIPD approaches which are currently TDM-centric and follow the path of the broader precision medicine initiative. The precision medicine landscape has grown dramatically during the 2 decades with diverse stakeholders, including hospitals and health care systems, biopharma companies, diagnostic and life science tools companies, commercial, academic, and hospital labs, as well as private investors.[21,22] Many academic centers of excellence offer degree programs in precision medicine as well. Likewise, the implementation of precision medicine solutions has required this stakeholder community to invest in platforms that facilitate the research, promote collaboration, and ultimately deliver solutions to patients,[23] particularly if AI integration is a credible component of the precision medicine strategy. A conceptual schematic framework for the key components of a precision medicine platform strategy is shown in the Figure. Central to the effort is the landscaping and access to all operational data stores within an institutional footprint. Such a landscaping effort must likewise be expandable as additional data of interest become known and available.

The AI and ML applications for precision dosing have much promise but have been evaluated only recently. Given the capability of ML to handle multidimensional data, such as those from EHRs, opportunities for AI

Table 1. Examples of Artificial Intelligence (AI) Integration Into Precision Medicine Practices

Clinical Opportunity	AI Approach and Application	Data Source(s)	Effect*
Microarray expression experiments have great potential for disease detection and diagnosis, but results are imprecise and uncertain[15]	Support vector machine and variants of the perception algorithms—learning algorithms used to classify expression data for normal and cancer patient tissues	Expression results for 97,802 cDNAs for various tissues (ovarian cancer, normal ovarian, and other normal tissues)	Improved prediction of success or failure of particular treatments theorized
Understanding phenotypic heterogeneity of HFpEF[16]	Unbiased hierarchic cluster analysis of and penalized model-based clustering, to define and characterize mutually exclusive groups making up a novel classification of HFpEF	Dense phenotypic data (phenomapping)	Allow targeted (and more successful) HFpEF clinical trials.
Need for improved diagnostic and therapeutic accuracy for cancer patients[17]	Pattern analysis and classification algorithms for improved diagnostic and therapeutic accuracy	Biomarker profile data from nanosensors	Proof of concept at the moment but many opportunities in a variety of cancer types
Diagnostic tool based on a deep-learning framework for screening patients with common treatable blinding retinal diseases[18]	Transfer learning (trains neural network)	Optical coherence tomography images	Expediting diagnosis and referral of treatable conditions, facilitating earlier treatment, resulting in improved clinical outcomes
More accurate illness risk prediction and improvements in diagnostic performance[19]	Multiple approaches, including machine learning, deep learning, and artificial neural networks, advocated	Multimodal phenotyping, including genomics, imaging, metagenomics, metabolomics, clinical testing, and family history data	Improved prediction of success or failure of particular treatments and disease diagnosis theorized
Assessment of motor performance in individuals with PD[20]	Hand-tracking model to locate the key points of the hand, enabling continuous tracking of finger-tapping angle incident by the thumb fingertip, the wrist, and the index fingertip; AI model assesses severity score	250 participants (172 with PD, 78 control) completing a finger-tapping task	Possibility of evaluating individuals with PD and other movement disorders remotely, objectively, and in areas with limited access to neurologic care

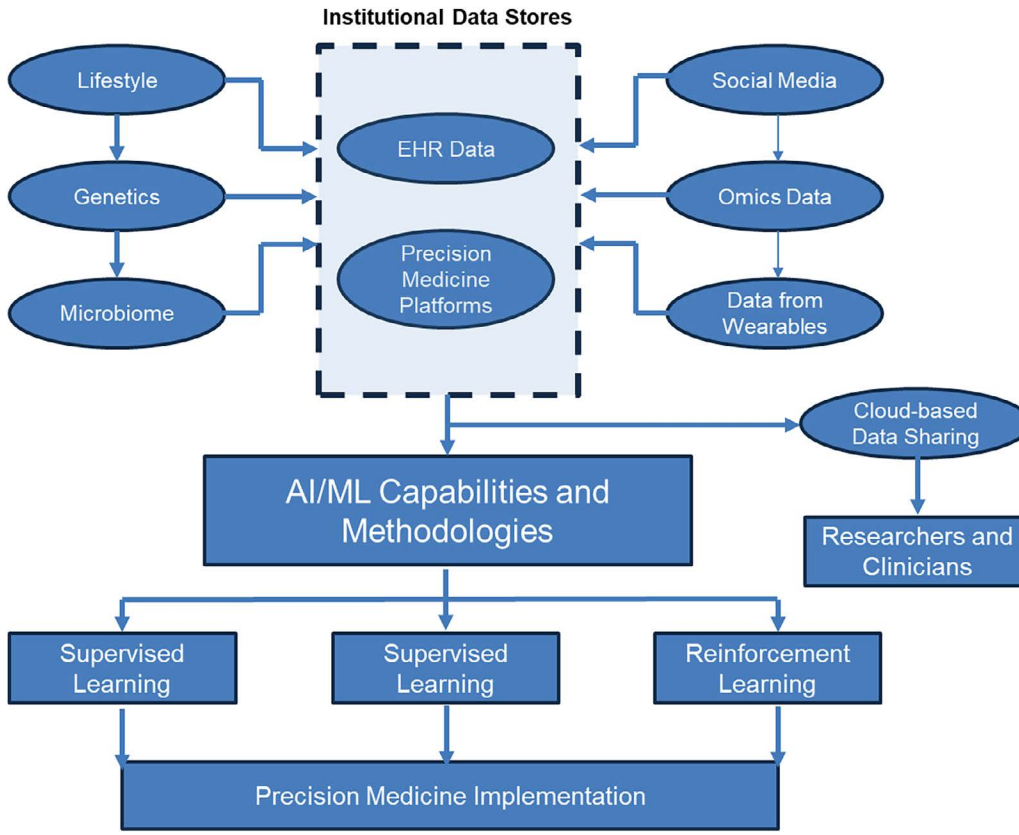
HFpEF, heart failure with preserved ejection fraction; PD, Parkinson disease

* Effect refers to actual or theoretical because many of these examples are early-stage efforts or proposals.

and ML applications to facilitate TDM and MIPD may be advantageous. Poweleit et al[24] promote collaboration citing that successful implementation of these approaches will depend on cross-field collaborations among clinicians and experts in informatics, ML, pharmacometrics, clinical pharmacology, and TDM. It is likely that this multidisciplinary approach will also need to include statistics, bioinformatics, and significant data science engagement as well.

Population PK/PD modeling, the central methodology of pharmacometrics and the backbone of TDM-based precision dosing solutions, estimates drug exposure

Figure. Artificial intelligence (AI) integration into institutional precision medicine strategy.



and efficacy over time in patients at the population level, or rather how the average patient responds to the drug. This approach allows for parameters associated with a drug to be quantified (e.g., clearance and volume of distribution), describes interindividual variability in drug PK/PD, and identifies predictive covariates. Another component of the pharmacometrics paradigm includes performing simulations to evaluate target attainment at given doses. Comparatively, ML focuses on making the most accurate predictions of outcomes. Although population PK/PD modeling can be considered a form of ML, a distinction between the 2 lies in the types of models used. The population PK/PD modeling approach commonly relies on developing structural models based on PK/PD concepts to provide pharmacologically and physiologically reasonable parameter estimations, whereas ML focuses on minimizing the prediction error using the most applicable model.

Although the integration of pharmacometrics and AI approaches has only recently gained traction, applications intersecting these 2 approaches actually date back to the 1990s, with several studies applying neural networks to PK/PD analyses and systems.[25–27] Because these applications are increasing, it is important to note that ML will not replace, but will rather complement, traditional pharmacometric approaches to achieve the goals of precision dosing, as previously stated. Understanding the research question and determining what tools are needed to address that question are important in determining when to use ML, traditional pharmacometric approaches, or a combination of both.

One of the many benefits of integrating AI approaches into existing and future precision dosing solutions is the ability to cope with diverse, large, unstructured data sources. Beyond a simple TDM-driven precision dosing strategy, AI integration provides a mechanism to deal with imaging data, data from other EHR sources, genomic data, etc.[28] Part of the challenge is that many of these non-traditional data sources do not always exist in the institutions' EHR systems, making data identification, curation, and integration an additional challenge. Moreover, most of the available platforms[29] do not offer this capability at present, although it is unlikely that this situation cannot be remedied.[30] Table 2 provides some initial thoughts on AI-enhanced precision dosing opportunities across a broad array of therapeutic areas. Some of these are conceptual, whereas others represent areas where applications already exist.[31]

Some of the examples mentioned in Table 2 relate to biomarker data (e.g., INR, hemoglobin A1c, immunoglobulin E, etc.), which indeed may be found in the

Table 2. Expansion of Traditional Precision Dosing Implementation Possible With Future Artificial Intelligence (AI) Integration and Deployment

Therapeutic Area	AI Application	Relevant Data Sources Required
Anticoagulation	Assess bleeding risk based on historical data conditioned on individual INR data	Clinical INR data relative to anticoagulant dosing and clinical outcomes (e.g., bleeding or other AEs)
Diabetes	Assess hypoglycemia risk based on historical data conditioned on individual HbA1c data	Hemoglobin A1c data relative to antidiabetic dosing and clinical outcomes (e.g., hypoglycemia or other AEs).
Asthma	Assess free IgE exposure based on historical data conditioned on individual weight, asthma severity, and dosing data	Optimize omalizumab dosing for individualized target serum IgE reduction
Tuberculosis	Individualization of antibiotic combination and dosing through therapeutic drug monitoring and in treatment biomarker levels to customize therapy duration	Evaluation of gene expression, genetic, epigenetic, metabolism, and/or immune phenotyping to discern the host endotype with endotype-specific host-directed therapies to shorten and improve clinical outcomes
Oncology	Many, including the prediction of several clinical outcomes (e.g., survival outcomes) of ovarian cancer patients through the combination of copy number aberration, and epigenome and transcriptome data sets using a model that extracts predictive patterns from both labeled and unlabeled samples and the prediction of glioblastoma progression based on integrated analysis of DNA methylation and matched imaging data	Integrated analysis of multiple types of omics data (e.g., transcriptomics and proteomics)

AE, adverse event; IgE, immunoglobulin E; INR, international normalized ratio

EHR system and be incorporated into traditional PK/PD approaches without necessitating an AI approach.

The future of model-based precision dosing (MIPD) will certainly require a more expanded approach and implementation beyond PK-centric models with TDM data as the only input source. One of the obvious areas of expansion is the incorporation for non-traditional data types beyond TDM. Within the biomarker arena this would include genomic and imaging data of various kinds.[32–34] These data types create challenges from the standpoint of data quality assessment, data curation, and integration with other traditional data sources used for MIPD development and deployment.

On a global basis, nations have invested in creating an electronic patient care environment to measure and improve health care quality (at both the individual and population levels), and to control costs.[35,36] In the United States, the Health Information Technology for Economic and Clinical Health (HITECH) Act was passed in 2009, as part of the American Recovery and Reinvestment Act.[33] As a result of the HITECH Act, and associated funding, by 2014 a total of 97% of US hospitals possessed EHR software and 75% had implemented EHRs.[37] Among office-based physicians in 2013, an estimated 78% of office-based physicians used some type of EHR, an increase from 18% in 2001.[38]

The EHR includes substantial patient-specific information, including demographics, diagnoses, laboratory results, procedures, medications, results of imaging studies, and clinician notes. The EHR interfaces with applications that are important for the delivery of patient care, including a computer provider order entry (CPOE) system and clinical decision support tools. The CPOE system allows the prescriber to select the treatment regimen (drug, formulation, quantity, duration, and dosing instructions), which is then recorded in the EHR and simultaneously sent to the pharmacy, where the medicine is dispensed for the patient. Each institution's EHR installation is unique to its environment and the vision of its IT leadership. In some cases key data are stored in locations outside the EHR, and there are many custom configurations where external applications are connected to the EHR via a custom application programming interface. Clinical decision support tools can either be written into the EHR system or be a standalone application programming interface (API). They are intended to help the clinician improve the quality of care for each patient by using their personal

information to improve diagnosis and treatment accuracy and effectiveness. Software components aligned with the EHR should work together seamlessly.

Integrating AI approaches and methodologies will be an important component of an evolving MIPD landscape, particularly as the individualized dosing emphasis expands beyond a TDM-centric based approach as in part of a larger precision medicine initiative. The integration will include both data and methodology requirements with desired seamless integration and the same rigor on qualification and validation assumed with current MIPD implementation. The ideal setting for such integration would be a collaborative approach with the data and methodology requirements challenged and agreed to by a global, multi-institution group of stakeholders for transparent collaboration. In this regard AI integration would also benefit from inclusion with commercial MIPD and EHR vendors to ensure the seamless aspects of future solutions is addressed as well as the continuity of existing solutions for the existing customer base.

Article Information

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