Artificial intelligence/machine learning: the new frontier of clinical pharmacology and precision medicine

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Artificial Intelligence/Machine Learning: The New Frontier of Clinical Pharmacology and Precision Medicine

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In recent years, artificial intelligence (AI) and machine learning (ML) have emerged as transformative forces driving innovation across various sectors. This themed issue of *Clinical Pharmacology & Therapeutics* (*CPT*) is dedicated to AI/ML Innovations (**Figure 1**), showcasing a wide range of opportunities for applying these technologies in clinical pharmacology. AI/ML enable the application of novel methods to potentially enhance the efficiency of drug discovery and development, as well as to optimize patient care (**Figure 2**).[1–5] This issue comprehensively explores their current applications in clinical pharmacology, addresses the challenges in their adoption, and discusses their potential to revolutionize future drug development and healthcare practices. By bringing together insights from leading experts and groundbreaking research, this issue aims to illuminate the path ahead.

APPLICATIONS OF AI/ML IN CLINICAL PHARMACOLOGY

The application of AI/ML in clinical pharmacology has been expanding rapidly in recent years. Shahin *et al.*[6] conducted a review of the use of AI/ML in clinical pharmacology, showcasing their various applications and the impact of successful AI/ML implementation during drug development and/or making regulatory decisions. Their review identified significant growth of interest in applying AI/ML within the clinical pharmacology and pharmacometrics community as evident from the recent spurt in publications.

The use of AI/ML in drug discovery is becoming increasingly prevalent. Taylor-King *et al.*[7] discuss how ML can be applied in target identification for drug discovery/development by focusing on causality, reversibility, and druggability. They discussed ML's potential yet moderate impact in target identification to date and emphasized the need for an integrated approach that combines ML with genetics and structural biology. The authors advocate for the use of ML in conjunction with contemporary biotechnologies, aiming to enhance our understanding of causative biology and reduce the high failure rates in drug development.

The modeling community has also been exploring AI/ML as a new tool. The Innovation and Quality (IQ) Consortium held an AI/ML workshop in 2022 with the aim of promoting the acceptance of AI/ML in model-informed drug discovery and development among the scientific community as well as by regulatory agencies.[8] The White Paper[9] published in the current issue builds on this workshop and further shares the consortium perspective on use cases and best practices. The White Paper

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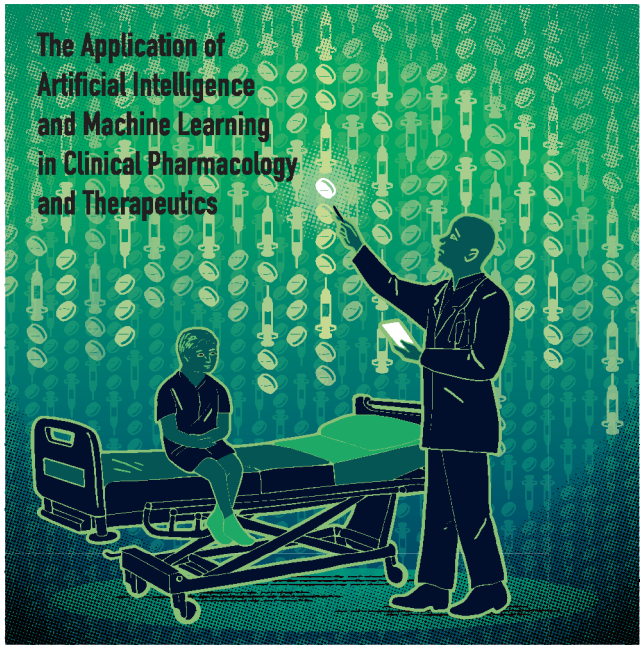

Figure 1 *Clinical Pharmacology & Therapeutics* April 2024 cover image: The Application of Artificial Intelligence and Machine Learning in Clinical Pharmacology and Therapeutics.

covers multiple areas, such as AI/ML in pharmacometrics, explainable AI (XAI), natural language processing (NLP), and drug discovery applications. The authors suggested incorporating relevant domain knowledge into the AI/ML formalisms to enhance its generalizability. Huang *et al.*[10] examined the use of AI/ML in pharmacokinetic-pharmacodynamic (PK-PD) modeling, proposing that although entirely replacing traditional models with AI/ML may not be feasible/advisable, a hybrid approach of AI/ML with existing PK-PD models could balance predictive capabilities with essential biological insights. They noted that AI and ML could efficiently process large datasets, detecting trends and patterns that might not be immediately apparent through conventional analysis. Consistent with this theme, Smith *et al.*[11] discuss a hybrid machine-learning PK/PD/toxicodynamic (ML-PK/PD/TD) approach to optimize combination therapy using human PK/TD data along with *in vitro* PD data. Li *et al.*[12] provide a Tutorial for pyDarwin, an open-source Python package that combines ML with NONMEM for nonlinear mixed-effect model selection. Terranova and Venkatakrishnan[13] conducted a Mini-Review on ML in modeling disease trajectory and treatment outcomes, including examples across various therapeutic areas such as neurology, rare diseases, autoimmune diseases, oncology, and immuno-oncology.

One of the most promising applications of AI/ML is to advance precision medicine. Based on the presentations at a February 2023 virtual public workshop entitled "Application of Artificial Intelligence and Machine Learning for Precision Medicine,[14]" hosted by the US Food and Drug Administration (FDA) and University of Maryland Center of Excellence in Regulatory Science and Innovation (M-CERSI), Naik *et al.*[15] discuss the use of AI/ML in precision medicine (e.g., prognostic and predictive factors identification, patient response prediction to support dose optimization, and patient population for treatment). It is worth mentioning that this paper also includes an overview of the AI and ML-related regulatory submissions to the FDA's Center for Drug Evaluation and Research in the years 2016 to 2022. A remarkable increase in the number of submissions has been observed in recent years. In some of these submissions, AI/ML was proposed to facilitate enrichment trial design, to stratify patients with different safety risk, to select or optimize dosing, or to ensure adherence to the assigned dosing regimen. Liu *et al.*[16] report a case in which the FDA used AI/ML for regulatory decision making—identifying the patient population for Emergency Use Authorization for anakinra for the treatment of coronavirus disease 2019 (COVID-19) in hospitalized adult patients. Curth *et al.*[17] reviewed the application of ML to estimate the expected Conditional Average Treatment Effect

Figure 2 Opportunities for the application of artificial intelligence (AI) in drug discovery, drug development, and patient care. (Disclosure: The artwork was generated using OpenAI's GPT4 model.)

in individual patients using observational data, and they concluded that ML holds great potential for estimation of the expected treatment effects in each patient based on their individual characteristics. Ding *et al.*[18] applied ML to data from two phase III trials and found that integrating longitudinal serum lactate dehydrogenase data with baseline risk factors can improve survival prediction in patients with metastatic colorectal cancer. Harun *et al.*[19] applied ML to data from four phase III trials and found key prognostic factors that impact remission in patients with ulcerative colitis. The findings could be leveraged to support exposure-response analysis and patient stratification for future trials.

AI/ML is particularly useful for NLP in our information-rich era. Hsu *et al.*[20] explored its use in clinical pharmacology, focusing on three case studies: dose optimization in oncology, identifying common covariates for PKs in oncology, and using physiologically-based PK analyses for regulatory review and product label. Verweij *et al.*[21] discussed an NLP approach to cluster sentences extracted from the sections on uncertainties in European public assessment reports of centrally authorized medicines, as a stepping stone toward a unified way of communicating uncertainties identified during the European Medicines Authorization process to the broader public.

In summary, from drug discovery and development to regulation and patientcare, AI/ML can streamline and enhance traditional processes, leading to more efficient and effective results.

CHALLENGES AND GAPS

Despite their potential, the integration of AI/ML in clinical pharmacology is not without challenges. Issues such as data availability/quality, bias, model generalizability, model opacity, model validity, and reliability pose hurdles to the development and/or application of the AI/ML model. In addition, ethical and legal considerations, particularly around patient data privacy, require careful navigation.

AI/ML, especially deep learning, can be data hungry. The model performance depends heavily on the data quality and quantity. However, the data availability and quality can be a challenge, especially due to the fact that medical data is often subject to strict privacy regulations, can be fragmented across different systems/institutions, and may vary greatly in format and standardization as well as data accuracy/completeness. Data sharing is immensely beneficial, yet it often presents significant challenges. Federated approaches (including federated learning) have been proposed for collaboration while protecting data privacy.[15] Synthetic/simulated data could also be useful. Zwep *et al.*[22] discuss the use of Copula models to simulate realistic patient characteristics in higher dimensions,

retaining the dependence structure between patient's covariates.

The previously mentioned IQ White Paper[9] in this issue of *CPT* notes that "Although AI/ML can unlock many opportunities, it is important to be cautious when using these advanced algorithms to avoid deriving biased and nongeneralizable conclusions from data." Gray *et al*.[23] discuss bias in AI, which is a growing concern in the field. The authors reviewed the current research on AI bias, including its sources, and the methods used for its measurement, benchmarking, and mitigation, with a focus on the healthcare field and regulatory science. Li *et al*.[24] conducted a systematic review of the application of ML for dose individualization. They found issues like inappropriate participant exclusion, small sample sizes, and mishandled missing data, leading to methodological flaws and bias risks in these studies. Additionally, the absence of external validation and clinical utility assessments limited the practical use of ML in dose individualization in the clinical setting. They provide 11 recommendations (e.g., representativeness of the data, external validation in independent datasets, etc.) to improve the clinical relevance of the studies and facilitate the translation of ML models into clinical practice.

Model opacity, characterized by a lack of interpretability and explainability, can significantly erode trust in AI/ML models, thereby impeding their practical application. Advancements in XAI methods[19] hold substantial potential to mitigate these challenges, enhancing transparency, and user confidence in these models.

Model validity and reliability are crucial in AI/ML applications. However, many publications on AI/ML for health applications suffer reproducibility issues.[25] In addition, AI/ML models are often vulnerable to adversarial attacks, such as strategically constructed inputs to deceive the system. Finlayson *et al*. demonstrate that subtle alterations in medical images could mislead diagnostic algorithms.[26] Concerted efforts are essential to enhance model robustness and ensure reliable performance in practical healthcare settings.

In their Artificial Intelligence Risk Management Framework,[27] the National Institute of Standards and Technology outline key characteristics of trustworthy AI, encompassing "valid and reliable, safe, secure and resilient, accountable and transparent, explainable and interpretable, privacy-enhanced, and fair with harmful bias managed." The framework also noted that "when managing AI risks, organizations can face difficult decisions in balancing these characteristics."

CALL FOR COLLABORATION

The advancement of AI/ML in clinical pharmacology has been largely fueled by interdisciplinary collaboration. Partnerships among clinical pharmacologists/pharmacometricians, clinicians, statisticians, data scientists, bioinformaticians, patient groups, and other stakeholders have been crucial in developing and validating AI/ML algorithms for clinical pharmacology. Coroller *et al*.[28] share a scientific collaboration between Novartis Pharmaceuticals Corporation and the FDA applying ML to analyze multi-omics data. The authors outlined practical steps for managing multi-omics projects involving cross-disciplinary teams from various institutions. They emphasized the importance of "ensuring efficient communication." In the AI/ML discussion paper released by the FDA in 2023, the FDA emphasized that "communication and engagement with patients and the public regarding considerations for AI/ML in drug development is critical to ensure patient-centered approaches and policies."[29]

The IQ White Paper[9] noted "effective collaboration among industry partners, academia, and regulatory agencies is essential to fully understand and harness its potential." Naik *et al*.[15] also included a call for action in their paper, encouraging "the sharing of data, algorithms, and experiences among the community," as well as "development of best practices and regulatory guidances" and "working with broad stakeholders."

FUTURE DIRECTIONS

AI/ML stands at the forefront of a new era in clinical pharmacology and precision medicine. Looking ahead, the potential of AI/ML in clinical pharmacology and precision medicine is boundless. As AI/ML continues to evolve and become increasingly more powerful, they will have a deeper integration into drug discovery, drug development, drug regulation, and personalized medicine.

The application of AI/ML in clinical pharmacology has its own challenges. These challenges, however, have catalyzed further innovation, with ongoing research focusing on various topics such as federated learning, privacy safeguard approaches, XAI, bias

measurement and mitigation, and ethical AI use in health care. The continued evolution and integration of these technologies holds immense promise for the future, heralding a new age of therapeutic development and health care.

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DISCLAIMER
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