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Pharmacogenomics and Personalized Medicine: Leveraging AI and Machine Learning for Optimized Therapies

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ABSTRACT: To examine how artificial intelligence (AI) and machine learning (ML) can advance pharmacogenomics and personalized medicine by improving drug-response prediction, treatment selection, dosing, and clinical decision support, while identifying the major barriers to clinical implementation. This narrative review critically synthesizes current applications of AI-enabled pharmacogenomics across oncology, cardiovascular medicine, psychiatry, and other therapeutic areas. It evaluates classical ML, deep learning, transformer models, unsupervised learning, federated learning, explainable AI, knowledge graphs, multimodal data integration, and electronic health record–based clinical decision support. Clinical applications, implementation requirements, ethical concerns, regulatory issues, and future research priorities are comparatively examined. AI and ML can integrate genomic, multi-omic, clinical, environmental, and longitudinal data to identify gene–drug associations, predict therapeutic efficacy and adverse drug reactions, optimize individualized dosing, and support genotype-guided prescribing. Evidence from oncology, cardiology, and psychiatry indicates that these approaches may improve patient stratification and treatment selection. Their integration into electronic health records and clinical decision support systems can enable timely, actionable recommendations. However, clinical translation remains constrained by limited and ancestry-biased datasets, inconsistent phenotype definitions, missing data, overfitting, class imbalance, weak external validation, limited interpretability, workflow incompatibility, clinician training gaps, privacy risks, algorithmic bias, and evolving regulatory requirements. AI-enabled pharmacogenomics has potential to support safer, more effective, and individualized therapy. Broad clinical adoption requires diverse standardized datasets, externally validated and explainable models, interoperable health information systems, ethical and regulatory governance, clinician education, and interdisciplinary collaboration. Federated learning, multimodal architectures, and continuous-learning systems may enable equitable, real-time pharmacogenomic decision-making.

1. INTRODUCTION

Pharmacogenomics is a foundational pillar of precision medicine, investigating the influence of genetic variation on individual drug response. This field seeks to optimize therapeutic regimens by aligning implementation of treatment options based on an individual's genetic makeup will help reduce the risk of adverse drug reactions and improve how well drugs work [1]. The

variation in genes affecting drug metabolizers, drug transporters and target receptors has led to variations in how drugs are processed by individuals which leads to variations in treatment responses.[2] The genetic differences among individuals result in varying levels of drug effectiveness or side effects; therefore, there has been interest in incorporating pharmacogenomics into clinical decision making.

There has been increasing evidence regarding the benefits of utilizing pharmacogenomics to guide medication prescriptions. Studies have shown improvements in treatment outcomes and cost-effectiveness when pharmacogenomics are applied to certain medications such as abacavir, mercaptopurine and tacrolimus.[3],[4],[5] Several organizations including the Clinical Pharmacogenetics Implementation Consortium (CPIC) and the Dutch Pharmacogenetics Working Group (DPWG) have developed guidelines based upon pharmacogenomics to provide clinicians with resources for making genotype-driven decisions.[6],[7],[8],[9] Despite this, many obstacles exist limiting broad application of pharmacogenomics into clinical practices including technology, education and infrastructure issues[10],[11].

The use of artificial intelligence (AI) and machine learning (ML) present opportunities for overcoming the current limitations of implementing pharmacogenomics. AI/ML have the ability to analyze large amounts of heterogenous data; therefore they can be used to uncover genotype-phenotype associations that would likely remain undiscovered using conventional statistical methods.[12],[13] Random Forests, Gradient Boosting Machines and Deep Learning Architectures are examples of ML algorithms that have been utilized for predicting drug response phenotypes, identifying subgroups of patients who could benefit from specific treatments and detecting potential gene-drug interaction using genomic and clinical data.[14],[15] AI/ML algorithms can also incorporate multiple types of data including genomic data, transcriptomic data, proteomic data and environmental data to increase the precision of therapeutic recommendations.[16],[17].

Recent research is demonstrating that applying transformer-based architectures and employing attention mechanisms will be able to advance both interpretability and prediction for pharmacogenomic modeling [18]. Researchers are currently developing integrative approaches utilizing AI to merge EHRs with structured/semi-structured data, and omic datasets into unstructured clinical text, allowing for real time pharmacogenomic decisions to be made [19] [20] [21]. Federated learning as well as privacy preserving AI methods also enable multiple sites to develop and test collaborative models without sharing central repositories of their data; therefore, protecting patient's rights while increasing the number of diverse datasets available [22].

Research exploring AI applications in pharmacogenomics and precision medicine continues to grow [23][24][25]; however most current reviews are either methodologically focused or clinically domain focused and provide no unified view of how advanced AI models can integrate multimodal data in a clinical deployment framework. Many of the publications detailing these studies continue to be descriptive, rather than methodologically critical and do not adequately evaluate the limitations associated with translating these findings to real world healthcare environments [26], [13].

The review aims to bridge those gaps with an in-depth and systematic examination of AI-based pharmacogenomics. Unlike previous studies that have discussed some combination of the aforementioned topics, but not all in one study; this review is the first to combine an overview of how to apply advanced AI technologies to generate clinically relevant information using multiple types of data for clinical decision-making systems, as well as discussions about how to deploy such systems in a real-world setting. In addition, this review includes an end-to-end depiction of the complete process for developing models based on data acquired through clinical practice and providing individualized recommendations regarding appropriate therapies or medications, followed by integrating them into patient care settings. Moreover, this review will provide an evaluation of each challenge identified as being significant for the application of AI-enabled pharmacogenomics systems including data bias, model interpretation, regulatory uncertainty, and clinical acceptance [26] [24]. Using case studies in cardiology, oncology, and psychiatry this review will illustrate both potential benefits and current limitations associated with applying AI-enable pharmacogenomics systems. Finally, this review will outline future areas of investigation to enable large-scale implementation of explainable and fair AI-based pharmacogenomics systems; and thereby advance the goal of achieving personalized medicine.

2. PHARMACOGENOMICS: AN OVERVIEW

2.1 Foundational Principles

Pharmacogenomics is an area of research that examines the relationship between genomic variation and drug effectiveness, toxicity, and metabolism. Pharmacogenomics has introduced a new paradigm for delivering care by moving away from a "one size fits all" model of care delivery to a more personalized model of care delivery based upon the individual's genetic make-up

to guide the provider in making clinical decisions [10] [11]. Key to this field is the concept that SNPs, gene duplication/deletion events, etc. will alter the functioning of genes important to pharmacokinetics/pharmacodynamics, thereby affecting how individuals respond to medications [2].

Some of the best characterized pharmacogenomic loci include genes involved in drug metabolism (such as members of the cytochrome P450 family [i.e. CYP2D6; CYP2C9/CYP2C19; CYP3A4/5]), genes involved in drug transport [e.g. SLCO1B1], and genes related to the immune system [e.g. HLA-B]. The example of polymorphism in the CYP2D6 gene shows the potential for alterations in a person's ability to convert codeine into morphine resulting in either toxic levels of morphine in persons who have reduced metabolic capability and therefore experience severe side effects/treatment failures, or, conversely, inadequate therapeutic effect in those with enhanced metabolic capabilities [27]. In addition, certain alleles of TPMT/Nudt15 show significantly diminished enzyme activity which can lead to severe myelosuppression during treatment with thiopurines [28] [29].

Beyond the classic examples that have been discussed, pharmacogenomic variation has an impact on how drugs are transported, bind to receptors and illicit drug-specific immune system responses for example, there are different drugs that have different types of transporters in our body. Some of these include drug transport protein genes such as (ABCB1 and SLCO1B1). Variations in the genes encoding drug transport proteins will influence how a drug is distributed within the body. Polymorphisms in the drug target genes can also influence whether or not the drug works. These multi-layered genetics drug response illustrates the complexity associated with drug response prediction.

It demonstrates why we need to develop more sophisticated computer models that integrate both drug transport protein gene variation and drug target gene variation when attempting to predict an individual's drug response.

Pharmacogenomics has evolved from focusing on single-gene influences to systems biology; therefore, it takes into account interactions among genes and environments [16] [30]. In addition, with advancements in technologies related to transcriptomics, epigenetic analyses and proteomics, pharmacogenomics is incorporating all of these "omics" types of data to build polygenic risk models and predictive signatures [31]. Polygenic risk models and predictive signatures are particularly useful when there are many factors involved (multifactorial) in disease states, such as those found in psychiatry and cardiovascular diseases. Drug response in these areas is influenced by large-scale complex biological networks rather than individual variants.

The development of multi-omics integration methodologies has allowed researchers to expand their use of pharmacogenomics through the ability to simultaneously analyze genomic, transcriptomic, proteomic and metabolomic data. Multi-omics integration provides a much broader view of biological pathway(s) responsible for influencing drug response. Therefore, the use of multi-omics integration is increasing rapidly as a means of identifying new biomarkers and therapeutic targets [17]. Additionally, the advancement of precision medicine past the current paradigm of single-marker based medicines is dependent upon continued development of multi-omics integration methodologies.

2.2 Current Applications

Pharmacogenomics has been implemented clinically over the past ten years in many areas of medicine, including oncology, psychiatry, cardiovascular disease, and infectious diseases. Pharmacogenomic testing for the use of certain chemotherapeutic agents has become a routine practice within oncology. These include the use of genotyping for DPYD to direct treatment with fluoropyrimidine; the use of genotyping for UGT1A1 to direct treatment with irinotecan; and the use of genotyping for EGFR and BCR-ABL mutations to determine which patients will respond to treatment with tyrosine kinase inhibitors [32], [33]. Psychiatry is another area where pharmacogenomics is being applied. Variations in genes that encode for cytochrome P450 enzymes, such as CYP2D6 and CYP2C19 have been shown to affect how well some patients respond to various classes of psychotropic medications, including antidepressants, antipsychotics, and mood stabilizers. Some research suggests that using pharmacogenetic tests to identify genetic differences that may influence a patient's response to these medications may be useful in reducing the incidence of side effects associated with medication, as well as improving the rate at which symptoms resolve [34], [35].

There is considerable clinical interest in applying pharmacogenetics to cardiovascular disease. An example includes those patients who carry loss-of-function alleles in CYP2C19; they do poorly with clopidogrel, resulting in an inability to adequately inhibit platelet aggregation and necessitating alternative antiplatelet therapy options, such as ticagrelor [36]. Another application of pharmacogenetics in cardiovascular disease involves the use of genetic screening for SLCO1B1 variants, as it allows clinicians to select safer statins and lower doses to reduce the risk of developing statin-induced myopathy [37]. The use of HLA allele

screening has revolutionized the way we approach safe practices in clinical settings related to infectious diseases. Examples include testing patients for HLA-B*57:01 before starting them on abacavir therapy and testing patients for HLA-B*15:02 before starting them on carbamazepine therapy. Both practices are now standard clinical procedures [3], [38].

Pharmacogenetic biomarkers that provide real-world guidance on drug choice and dosage are being increasingly implemented clinically (Table I). Several of these biomarkers now demonstrate the success of translational genomics to practical clinical applications; they have been instrumental in increasing both patient safety and positive clinical outcomes. Public pharmacogenetic databases have enabled the translation of clinical pharmacology. For example, PharmGKB is a database containing compiled information about drug-gene interaction relationships, whereas Pharm Var is a repository with defined allelic variants [39]. A growing number of Evidence-Based Guidelines (EBGs) from both the Clinical Pharmacogenomics Implementation Coalition (CPIC) and the Dutch Pharmacogenetics Working Group (DPWG) are now being implemented in Electronic Health Records (EHRs), thereby allowing for real time decision-making [8] [9]. This trend is creating an environment where Genotype-Driven Prescribing will become a reality through Institutional Implementations including emerge Network and the IGNITE consortium.

In spite of this progress there remain many impediments to broader acceptance and use. Clinicians' lack of knowledge about PGx, the lack of standardization for clinical work flow processes, and the challenge of successfully implementing pharmacogenetic information into electronic health records are just a few examples of the barriers which exist [10]. Moreover, because there is considerable variability in genetic architecture among different ethnic and racial groups, there is concern regarding how pharmacogenomic recommendations may be applied universally, making it important to develop more inclusive datasets that represent diverse populations.

3. ROLE OF AI AND ML IN PHARMACOGENOMICS

Traditional statistics generally do not have the capability to handle the many types of data that are typically present when evaluating a drug's interaction with genes, including their non-linear and multi-variable characteristics. However, supervised learning is very well-suited for analyzing these same data. Specifically, supervised learning algorithms such as Support Vector Machines (SVMs), Decision Trees, Ensemble Models such as Random Forests, Gradient Boosting Machines; etc. are all able to evaluate how multiple genetic variants interact and affect various phenotypic traits [14] [15]. These models show promise in the ability to predict ADRs, Drug efficacy, and Metabolic Phenotypes using either Genotype or Phenotype Data.

Classical Machine Learning models are useful due to their interpretability as well as computational efficiencies; they may be easily incorporated into Clinical Workflows. Nevertheless, the performance of these models typically relies upon the quality of the input data and the quality of Feature Engineering performed. The Quality of the Input Data and the Quality of the Features extracted are highly variable among Pharmacogenomic Datasets. This variability has led to an interest in developing More Advanced Modeling Approaches capable of automatically extracting Meaningful Representations from Raw Data. The use of Deep Learning Techniques – including Convolutional Neural Networks (CNNs), Recurrent Neural Networks (RNNs), and Auto-Encoders – has increased the amount of information captured through Hierarchical Data Representation without the need for Predefined Features [40].CNNs were applied to Genomic Sequences, while RNNs are commonly applied in Temporal Models related to Pharmacogenomics/Electronic Health Records (EHR) [41].Both types of Architectures allow for the Capture of Nonlinear Relationships and Temporal Dependencies that Traditional Methods cannot.

Recent transformer architecture based on attention, e.g. BERT, and their biomedicine derivatives (e.g. Bio BERT, Pharm BERT), have demonstrated great potential in utilizing unstructured clinical narratives and scientific literature to extract pharmacogenomics related information [20][19]. These models utilize self-attention to find contextually relevant relationships between a gene, drug and clinical outcome. The use of these models can provide value when performing large scale EHR and biomedical corpus analysis to gain insights into pharmacogenomics where those insights are difficult to access.

Unsupervised machine learning techniques are equally important as they help discover hidden genetic groupings of populations, and pharmacogenetic traits that are undetectable with annotated data. Techniques such as principal component analysis (PCA), k-means clustering and t-distributed stochastic neighbor embedding (t-SNE) have successfully been used on large scale genomic datasets to identify how ancestry informs the distribution of alleles and group them based on their subgrouping characteristics [42]. The use of these unsupervised machine learning techniques is necessary to improve model performance by discovering population specific pharmacogenomics variation and increase the ability of models to be generalized fairly.

Additionally, federated learning frameworks have been introduced to train distributed AI models on the use of a "federated" approach allows researchers to access protected datasets from different institutions — without combining those datasets centrally — and thus protects both individual genomics data and the diversity of populations represented in research studies [22]. Federated approaches to machine learning are especially useful in health care because regulatory barriers and ethical concerns limit the sharing of large amounts of personal or identifiable health-related information.

In addition, by allowing researchers at various institutions to collaborate on developing their own predictive models through federated learning — all while protecting the confidentially of patients' medical records — this can improve the accuracy and robustness of those models while reducing barriers to collaboration. To increase the acceptance of pharmacogenomic predictive modeling among clinicians — and to help build that confidence — researchers have turned to explainable AI (XAI), such as using SHAP (SHapley Additive explanations) and/or LIME (Local Interpretable Model-agnostic Explanations) to enable clinicians to see what specific features of an individual's genetic or clinical profile influenced the model's prediction [43], [44]. Both SHAP and LIME allow users to identify which aspects of an individual's genetic and clinical profiles were most influential in predicting pharmacogenomic outcomes — but like many other XAI tools, they often operate after-the-fact — i.e., after the predictive model has been run.

AI-driven pharmacogenomic graphs (which use ontology) enable automated reasoning over biomedical ontologies to accelerate drug repositioning and biomarker discovery [45], as well as identify gene–drug associations and therapeutic opportunities by integrating diverse data sources, including genomic databases, clinical records, and the scientific literature.

A comparative summary of the types of AI/ML models used for each application and their contributions across various therapeutic areas is provided in Table I, illustrating the complementary roles of different AI technologies in pharmacogenomics. The selection of an appropriate model depends on the nature of the data, clinical objectives, and requirements for interpretability.

Table I: Applications of AI/ML Models in Pharmacogenomics across Therapeutic Domains

AI/ML Model Type	Application	Therapeutic Domain	Key Contribution
Random Forest, XGBoost	Drug response prediction, patient stratification	Psychiatry, Cardiology, Oncology	Predicts efficacy and ADR risk using multi-gene and clinical covari- ates [14], [15]
CNNs, RNNs	Feature extraction from sequence or EHR data	Oncology, Epilepsy, Infectious Disease	Enables deep phenotyping and longitudinal modeling of pharmacogenomic data [40], [41]
Transformer Models (BioBERT, PharmBERT)	NLP-based extraction from biomedical literature and EHRs	Cross-domain	Maps gene–drug relationships from unstructured text for CDSS integration [20], [19]
Unsupervised Clustering (e.g., k-means, t-SNE)	Population stratification, Allele frequency visualization	Population Genomics	Reveals ancestry-specific allele patterns, aiding equitable model training [42]
Federated Learning	Cross-institutional model training without central data pooling	Psychiatry, Oncology	Enhances privacy, improves model generalizability across health systems [22]

Explainable AI (SHAP, LIME)	Model transparency and clinical interpretability	All domains	Supports trust and understanding of AI-guided dosing or drug selection [43], [44]

AI/ML is being used to create Clinical Decision Support Systems (CDSS) that incorporate a person's genetic information to customize their treatment. The system uses a combination of a person's genotype; Drug-Gene Interaction Databases; and their clinical history to recommend drugs based on their genotype. It has been proven that when an AI/ML model is integrated into a CDSS, it will increase the ability of clinicians to make accurate prescriptions; decrease adverse drug reactions; and support pharmacogenomic testing prior to administration of medication [46] [47].

A multi-modal framework using multiple types of AI (genomics, transcriptomics, proteomics, etc.) and integrating environmental/lifestyle factors has been created to evaluate drug responses and to identify which patients would be most responsive to specific treatments. This multi-modal approach has improved predictive power for both drug response and identifying sub-populations within larger disease states (e.g., depression, epilepsy, and cancer) [48][49]; Additionally, Explainable AI methodologies (SHAP & LIME) assist clinicians in understanding the reasoning behind decisions made by ML-based systems [43] [44].

As AI technologies advance, their incorporation with real-world data sources like biobanks, EHRs, and wearable devices is anticipated to facilitate ongoing, adaptive learning systems that adjust to emerging pharmacogenomic insights. This progress presents opportunities for the widespread deployment of adaptable, privacy protecting, and interpretable pharmacogenomic systems.

4. AI/ML IN PERSONALIZED MEDICINE

4.1 Patient-Specific Drug Response Prediction

A crucial aspect of artificial intelligence (AI) and machine learning (ML) in personalized medicine is their capacity to predict individualized drug responses by integrating genomic, phenotypic, and clinical elements.In contrast to conventional statistical methods, MLmodels can identify nonlinear relationships in high-dimensional datasets, allowing precise evaluation of therapeutic effectiveness, ideal dosage, and likelihood of adverse drug reactions (ADRs) [50], [51] Models that include supervision — e.g. logistic regression, random forest, SVMs, and neural nets — have been successful at making predictions for a wide variety of pharmacogenomics applications — e.g., psychotropics, immunosuppressives, chemotherapy agents.

Predictive frameworks using supervised models are also being developed to use data from multiple input types — e.g. genome-wide association study (GWAS) variants, RNA expression patterns, demographics, and/or comorbidity information — with the goal of making more reliable and personalized predictions. Ensemble-based techniques have demonstrated improved model generalizability through integrating various models to identify different ways features may interact. The validity of these models depends heavily on how well the training set was created/collected; the degree of genetic diversity represented within the populations studied; and how well the models were validated against independent sets of test cases.

Predictive models combining CYP2D6, CYP2C19, and other patient-based clinical information have shown positive results in management of major depressive disorder (MDD) with the use of SSRI drugs by avoiding a number of ineffectively prescribed SSRIs [52]. Also, Deep Learning has been applied to predict Chemotherapy by incorporating both Somatic Mutations and Germline mutations [53]. The development of artificial intelligence (AI) based dosing system using VKORC1 and CYP2C9 as well as demographic data for individualizing warfarin treatment has resulted in better INR management and less bleeding episodes [54]. Recent studies on polygenic risk scores combined with machine learning (ML) classifier models to predict inter-patient variability in response to other classes of drugs such as anti-inflammatories and lipid lowering agents is an area of ongoing study [31][17].

4.2 Disease-Specific Applications

The use of AI-driven pharmacogenomics has produced notable advancements in various disease areas. In oncology, AI technologies currently incorporate gene expression profiles, tumor mutational burden, epigenomic markers, and

pharmacogenomic data to assist in the tailored selection of tyrosine kinase inhibitors, immunotherapeutics, and hormonal treatments [55]. Deep learning models have also been used to stratify responders to immune checkpoint blockade therapies using multi-modal biomarkers including HLA haplotypes, PD-L1 expression, and microsatellite instability. Recent developments in oncology further illustrate the potential of deep learning for predicting drug synergy and resistance mechanisms, enabling combination therapies that are more precise than ever before.

In psychiatric applications, pharmacogenomic algorithms are improved using artificial intelligence (AI) integration of clinical history information, environment exposure variables, and neuroimaging data due to variability in patient responses to treatment [56]. The development of machine-learning (ML)-based tools for use in clinical practice, including GeneSight and NeuroIDgenetix, have demonstrated a real-world clinical impact through optimization of initial antidepressant or antipsychotic prescriptions [57]. Deep learning prediction models for identifying seizure activity have also started to integrate pharmacogenomics with the goal of personalizing antiepileptic drug therapy for those who do not respond to standard treatments [58],[59].

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The use of AI in cardiovascular pharmacogenomics has also been on the rise. Besides anticipating inadequate clopidogrel response in CYP2C19 loss-of-function carriers, ML models are now utilized to project responses to direct oral anticoagulants (DOACs) and to assist in tailoring antihypertensive therapy by employing pharmacogenomic and comorbidity data [60], [61]. These developments emphasize AI's role in enabling real-time, genomics-driven clinical decision-making for complex diseases

4.3 Integration with Electronic Health Records (EHRs)

The inclusion of Pharmacogenomic Data within Electronic Health Records (EHR's) is an important step in providing individualized treatment at the time of care. Artificial Intelligence will be crucial in allowing the automation of Clinical Genomic Data Mapping to allow for actionable pharmacogenomic recommendations. By using natural language processing (NLP) techniques, especially with use of Domain-Specific Transformer Models, can enable the extraction of appropriate references regarding Gene-Drug Interactions; Metabolizer Status; Dosing Recommendations contained in clinical notes, discharge summaries, and pathology reports [62]. After extracting these types of information, they are populated into structured fields in EHR's and create alerts related to drug efficacy issues and Serious Adverse Drug Reaction (SADRs) risk that enables active clinical decision-making [63].

In addition, as shown in Figure 1, AI enabled pipelines provide the means to integrate pharmacogenomic data into EHR systems and provide Automated Decision Support and Real-Time Clinical Alerts. The integration of Pharmacogenomic Data into Routine Clinical Workflows through EHR systems is a major component of integrating Pharmacogenomics into clinical practices

The integration of artificial intelligence (AI) into Clinical Decision Support Systems (CDSS) has allowed for the interpretation of pharmacogenomic test data in real-time.

Many CDSS systems include Genotype Parsers, Guideline-based Logic (i.e., based on evidence statements from organizations like CPIC or DPWG) and AI-based Alert Mechanisms. There are many examples of this type of technology being implemented at Academic Centers around the country; e.g., Mayo Clinic, University of Florida, St. Jude Children's Research Hospital. The implementation of these technologies allows for the use of Preemptive Pharmacogenomic Testing and Point-of-Care Drug Selection [21] [64]. These types of technologies have resulted in an increase in Clinician Confidence, a decrease in Prescribing Errors, and an Improvement in Adherence to Pharmacogenomic Guidelines.

There are several AI-Enabled CDSS Platforms that are currently available to assist with both the application and development of pharmacogenomics in research and in clinical practice. A summary of some of the key platforms is outlined below in Table

II. This table outlines the Algorithmic Basis, Features, and Deployment Status for each platform. As shown by the variety of platforms listed above, AI provides a mechanism through which pharmacogenetic information may be converted into Recommendations that are actionable to Healthcare Providers in Multiple Settings.

In addition to providing a framework through which pharmacogenetic knowledge may be used to generate actionable recommendations to clinicians, AI-based Data Harmonization Approaches are also allowing for the Portability of Pharmacogenetic Data Across Institutions. For example, graph-based learning models (e.g., EigenPGx) are being developed to enable the Alignment of Disparate Electronic Health Record Formats and Genotype Annotation Standards. The alignment of disparate data formats will allow for Interoperable Models and Scalable Model Retraining [65]. Such data harmonization methods will provide the foundation upon which Cross-Institutional AI Systems May Be Developed and Continuous Model Improvements Can Occur.

Multi-modal AI systems have been created to combine genomic, transcriptomic, and proteomic information with environmental and lifestyle elements. These integrated models have shown enhanced effectiveness in forecasting drug responses and classifying patients, especially in intricate disorders such as depression, epilepsy, and cancer [48], [49]. SHAP and LIME, as explainable AI methods, will improve clinicians' ability to understand how an AI system made a recommendation and improve clinicians' confidence in using those recommendations (as shown by [43] and [44]).

The future will be comprised of continuous learning, based on real world data from biobank repositories, electronic health record (EHR) databases and wearable devices. The expectation is that these systems will evolve into adaptive systems; they will also preserve patient's private information, and provide explanations.

Table II: AI-Enabled Clinical Decision Support Systems for Pharmacogenomics: Features and Clinical Implementation

Tool / Platform	AI Functionality	Features	Clinical Deployment Status
GeneSight®	Rule-based + ML scoring	Antidepressant matching, incorporates CYP2D6/CYP2C19 genotypes	Commercially available; widely adopted in psychiatry clinics
YouScript®	NLP + evidence-based reasoning	Polypharmacy alerting, drug–gene–drug interaction detection	Integrated with several EHR systems (e.g., Epic, Cerner)
PharmCAT + CPIC CDSS	Genotype parsing + rules engine	CPIC guideline-based recommendations, PGx report generation	Research/development stage; EHR integrations underway
CNSDose™	Predictive ML modeling	Antidepressant dosing based on hepatic gene variants	Commercial clinical tool; validated in randomized trials
PG4KDS (St. Jude)	AI-aided flagging + manual review	Alerts for 12+ drugs, EHR-integrated alerts, pharmacist oversight	Fully implemented in pediatric oncology at St. Jude
eMERGE-PGx CDSS	NLP + data mining	Site-specific implementations with AI-assisted alerts	Piloted in multi-center research consortia

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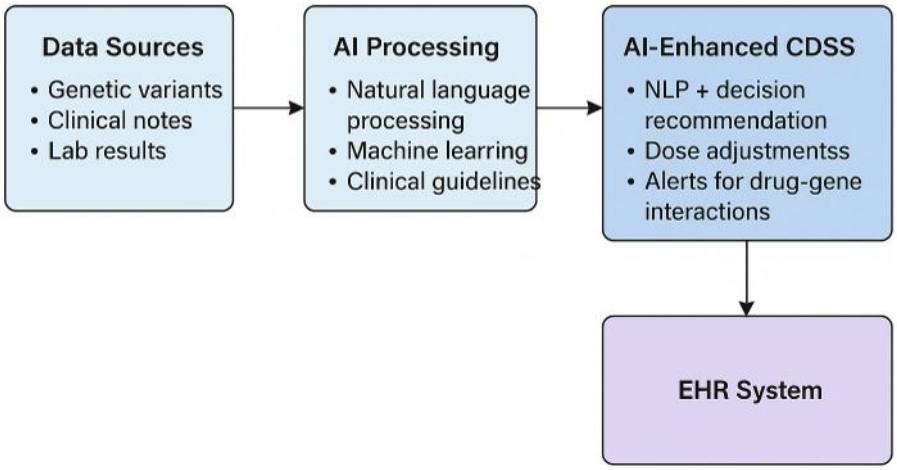

Figure 1: Integration of pharmacogenomic data into EHR systems using AI-enabled pipelines and decision support

5. CASE STUDIES AND REAL-WORLD EXAMPLES

5.1 AI in Oncology

Precision oncology projects are typically reliant upon NGS for identifying somatic mutations within genes that can be used to direct a targeted therapy; these include TKI's and mAb's directed toward genes such as EGFR, ALK, and KRAS [66] [67]. The use of pharmacogenomics via AI is also well established in the field of oncology due to the vast amount of multi-omic data available and the high expense and complexity of treatments used for cancer.AI algorithms have been employed to combine genomic, transcriptomic, and radiologic data to categorize patients, discover new therapeutic targets, and forecast treatment responses with greater precision than traditional bioinformatics methods [68], [10].

The ability of these A.I.-based methods to help address tumor heterogeneity will be important as it is still an issue with treatments for cancer. Machine Learning Models may better enable identification of subclonal mutations and prediction of resistance mechanisms by using Multi-Modal Data Sources (e.g., Genomic Sequencing Data, Radiomics Data, etc.). Furthermore, A.I.-based Survival Models are now being used to forecast prognosis in patients and to guide the optimal ordering of treatments.

One example of a case in which AI has been used as an enhanced decision tool to help determine optimal treatment based on trastuzumab is in treating HER2-positive breast cancer. These enhanced decision-making tools were created using HER2 protein expressions, PIK3CA gene mutations, and immune cells infiltrating the tumor [25] [67]. AI has also helped in predicting how well patients will respond to immune therapies such as PD1 and CTLA4 checkpoint inhibitors, based on Tumor Mutation Burden (TMB), MSI, and the genetic makeup of HLA haplotype [69] [11]. The use of Machine Learning Models to make recommendations about therapy for each individual patient are currently underway at both Memorial Sloan Kettering Cancer Center and Dana-Farber Cancer Institute and are being incorporated into clinical decision making at their Tumor Boards.

Although there has been advancement in moving AI-based Oncology Models from development to use within clinical practice, barriers still exist. Most models have been validated on retrospective data sets that have had little or no validation in external environments. In addition, lack of interpretability of complex model outputs can hinder clinical acceptance. Clinical oncologists need the ability to understand how the model arrived at its conclusions so they can make informed treatment decision.

5.2 AI in Cardiovascular Diseases

AI has played a critical role in Cardiovascular Pharmacogenomics in enhancing treatment of antithrombotics and anti-hypertensives. Clopidogrel usage for individuals receiving PCI is influenced by an individual's CYP2C19 genotype. Several studies have indicated that when an AI model utilizes both genetic information, demographic data, and procedural data it can better predict MACE and assist with the selection of prasugrel or ticagrelor in genetically predisposed poor responders [70],

[71]. Studies such as TAILOR-PCI and POPular Genetics have demonstrated the value of Genotype-Guided Therapy as it relates to both economics and clinical outcomes [72].

Beyond antiplatelet therapy, artificial intelligence models are also being used to predict cardiovascular risk and personalize treatment for a wide range of diseases including hypertension, heart failure and atrial fibrillation. These models use pharmacogenomic data combined with clinical and lifestyle factors that provide more precise stratification of risk as well as optimization of treatment.

Warfarin Dosing Optimization – Machine Learning Warfarin dosing can be optimized by machine learning models that take into consideration VKORC1, CYP2C9 genetic data as well as patient's age and body surface area. Studies have demonstrated these machine learning models are better than traditional dosing algorithms at lowering patients' risk for bleeding while simultaneously shortening their time to achieving a stable INR level [73][74]. The application of these models at academic institutions like the University of Florida Health System has led to reduced hospital readmission rates and fewer medication-related adverse events [64].

Although numerous predictive models have demonstrated statistical advantages over traditional clinical decision support tools, their clinical utility has not been consistently supported by evidence from real-world studies. Moreover, although there are efforts underway to integrate AI based decision support into various aspects of real time clinical workflow, it remains limited; therefore, there exists an urgent need for standardized validation and implementation methods.

5.3 AI in Mental Health

The use of Pharmacogenomics (PGx) in psychiatry is uniquely challenging because of polygenic inheritance of drug response and the inherent heterogeneity in how individuals respond to different drugs. However, Artificial Intelligence (AI) has had success informing treatments of depression and schizophrenia using commercially available software packages, including; GeneSight, CNS Dose and NeuroID genetix [75], which utilize machine learning (ML) to analyze an individual's genomic data – especially mutations in genes CYP2D6, CYP2C19 and SLC6A4 -- to provide recommendations for specific medication classifications and dosages.

There are real-world examples demonstrating the ability to achieve improved remission rates, lower medication switching and improved adherence to prescribed medications when PGx is used with AI-based decision support systems to treat Major Depressive Disorder (MDD) and bipolar disorder [57]. As a result of embedding this technology into their respective Psychiatric Evaluation Workflows at The University of Pittsburgh Medical Center and Mayo Clinic, these two organizations were able to decrease the time to achieve an optimal treatment response while also reducing the number of psychiatric emergency department visits [69] [10].

Recent advancements have further expanded the role of AI in psychiatry by incorporating neuroimaging data, behavioral metrics, and digital phenotyping into predictive models. Although these approaches represent an advancement toward better understanding of the complex factors that underlie psychiatric disorders —and will help personalize treatments— there is considerable heterogeneity within the evidence-base for AI-based pharmacogenomics applied to mental illness.

In contrast to several investigations which have reported statistically-significant clinical improvement(s), many other studies have found only modest differences between individuals treated with AI-based pharmacogenomics and those receiving usual (standard) care. Additionally, variability in both study-designs and sample-populations; as well as the measurement-outcomes, complicate interpretation.

5.4 Cross-Domain Insights and Translational Challenges

Common themes are emerging across oncology, cardiology and psychiatry. One theme is that AI-based pharmacogenomic models outperform statistical based models in predicting responses to drugs. Another theme is that using multiple types of data (genetic information; clinical data; environmental factors) improves the performance of the models by making them more robust and clinically relevant.

Despite the advances made with respect to AI-based pharmacogenomic models, there are still many obstacles to overcome for those models to be used widely in a clinical setting. Some of the major obstacles are that few have been externally validated,

there are no standard methods for evaluating how well they perform and it is difficult to incorporate AI tools into an existing health care infrastructure.

Other challenges include how to address data bias and interpretability of AI outputs as well as how to comply with regulations to move from the lab to use in the clinic.

In summary, these three examples provide a clear example of the promise of AI-based pharmacogenomics as well as some of its shortcomings. The upcoming actions will include creating standards for gathering and handling significant data volumes, verifying AI-driven pharmacogenomic models across different populations, and collaborating across fields to enhance our comprehension of the optimal integration of AI-driven pharmacogenomics in clinical environments

6. CHALLENGES IN AI/ML-DRIVEN PHARMACOGENOMICS

6.1 Data Challenges

The extent to which AI and ML can be effective in Pharmacogenomics will depend heavily upon the quality, quantity and diversity of available data. An important limitation in current practice is the limited availability of large scale, representative pharmacogenomic databases that relate genomic variation with clinical outcome across diverse populations.[10],[69] Most current datasets are from individuals of European ancestry; this limits the generalizability of many AI models and exacerbates health inequities for underrepresented populations.[11],[68].Research Program and the Global Alliance for Genomics and Health (GA4GH) aim to improve diversity, but these efforts are still in progress.

In addition to population bias, pharmacogenomic datasets are inherently complex and varied. The combination of multi-omics data (such as genomics, transcriptomics, proteomics, and epigenomics) with actual clinical data presents considerable technical difficulties. Absence of values, batch effects, and inconsistencies in data collection methods among institutions undermine model strength and reproducibility [13], [25].

In addition to this issue, another significant challenge with harmonizing the pharmacogenomic phenotypes (e.g., metabolizer status, drug effectiveness, etc.) is that they have not been standardized among the various research projects, thus hindering both training and testing of the models [8],[76].

Another developing problem area for pharmacogenomics is the dynamic characteristics of medical data. The way an individual responds to a particular drug may change during the course of their illness, through use of other medications and exposure to environmental factors; however, almost all pharmacogenomic databases represent the patient's response at one single point in time. Therefore, it can be difficult for artificial intelligence models to detect how the response to treatments changes over time and adapt accordingly. In order to address some of these problems associated with collecting/processing clinical data, researchers will need to develop robust processing methods, standardize terminology using ontological concepts and create federated machine learning platforms along with establishing standards for sharing clinical information.

6.2 Algorithmic Issues

Although AI/ML algorithms exhibit potential, their implementation in pharmacogenomics faces technical and methodological obstacles. A key concern is the absence of interpretability in numerous intricate models, especially deep neural networks.

Healthcare professionals need clarity to support their treatment choices, yet black-box algorithms frequently do not provide explanations that can be acted upon in a clinical setting [23], [24]. The development of XAI tools such as SHAP, LIME and the use of attention-based visualizations has helped to address the issue somewhat; however, there will always be trade offs to some degree regarding model accuracy vs. interpretability [77].

Model over fitting is also an area of concern, mainly due to the nature of high dimensional genetic data and low numbers of samples available for training. Pharmacogenomics may also present a problem related to gold standard labeled phenotypes (i.e. drug response or toxicity), which are typically expensive and labor intensive to produce [68] . Additionally, the most common type of data used for developing ML models is unbalanced (for example, the number of ADRs that occur during trials is typically much lower than the total number of patients enrolled in those same studies). Class imbalance can create a bias toward certain predictions and limits their applicability in the clinic [13]. Techniques to improve this include regularization methods (e.g. dropout, l1/l2 loss functions); data augmentation; and using multiple models (ensemble learning); all of these require rigorous cross-validation and external validation.

The increased focus on reproducibility is also due to issues with model replicability. This is because differences in what the training data set looks like; how that data was preprocessed; and how different researchers evaluate their models (i.e., metrics) are likely to produce varying results when comparing models across studies, as well as across various implementations of those studies.

Bias in model training and evaluation and bias that is present in data used for model training (and therefore model output) can also be an issue. Systemic biases in models may result from the same types of systemic inequalities that exist within the data (e.g., gender, ethnicity), which could result in dangerous or unfair recommendations [11] [10]. Therefore, there will need to be a transparent report on methods used in developing the model with guidelines similar to those outlined in the TRIPOD-AI (Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis: Explanation and Elaboration) document, as well as standardizing how a model's performance should be evaluated in clinical validation studies.

6.3 Implementation Barriers

There are several obstacles to translating AI-based pharmacogenomics into a standard clinical workflow. One obstacle is that many healthcare systems have no method of capturing, handling and querying genomic information along with their electronic health records (EHRs), in real-time [64] [8]. A second barrier is developing a means to incorporate an AI model into clinical decision-making support systems (CDSS) that will allow it to "talk" to the EHR's platform using a robust interoperable framework that can properly map genetic testing results into discrete and actionable outputs [69].

Another significant obstacle to use is the need for workflow integration. For an AI-based recommendation for pharmacogenomics to be effective, it must be provided in a timely manner; and in a suitable format; and as part of the physician's normal clinical decision process. A poorly designed interface or too many alerts can cause physicians to become fatigued with using the tool and therefore decrease its use, although the model may be technically correct. The complexity of regulations further complicates implementation. As noted previously, there is currently little agreement around the world regarding the validation and approval of AI-based pharmacogenomic models. Agencies such as the FDA and EMA have provided guidelines concerning clinical decision-support software but the frameworks continue to evolve slowly compared to rapid advances in technology [24]. There continues to be no standardization for documenting model development, evaluation, and continuous monitoring, which hinders regulatory approval and physician trust.

Clinical adoption is further complicated by the need for education on clinical use of clinicians, as well as through the need to collaborate with other disciplines. Studies have shown a large number of health care providers are lacking in their confidence when it comes to interpreting pharmacogenomic testing results (or even the recommendations generated by machine learning) [23], [10]. Thus, without educational programs directed at these specific areas, as well as participation from pharmacists, genetic counselors, and informaticians, there will be no realization of the potential of artificial intelligence in pharmacogenomics.

Table III: Summary of Key Barriers in AI-Enabled Pharmacogenomics

Category	Examples of Challenges
Data Challenges	Population bias, lack of phenotype standardization, data sparsity, missing values
Algorithmic Issues	Model interpretability, overfitting, class imbalance, bias propagation
Implementation Barriers	Lack of EHR integration, unclear regulatory pathways, clinician training gaps

These challenges highlight the gap between technological capability and real-world clinical application. Although AI-driven pharmacogenomics has demonstrated significant promise in controlled research settings, its successful implementation in routine clinical practice will require collaborative efforts in data standardization, model validation, regulatory alignment, and clinician engagement.

7. ETHICAL AND LEGAL CONSIDERATIONS

7.1 Privacy and Consent

AI in Pharmacogenomics also raises privacy, ownership and consent questions. Due to genetic information being able to be traced back to an individual's family, privacy violations and discrimination are much greater than other forms of data [10], [11] that do not include genetic identification. Even though data may have been removed from personal identifiers pharmacogenetic

data can be linked to identifiable databases such as ancestry profiling or Electronic Health Records (EHRs), potentially identifying individuals [69], [23]. The use of genetic data to identify individuals can lead to both technological breaches of security and privacy issues. While there have been many examples of technology being breached with regards to genetic information that was stored in genomic repositories (forensic genomics), the fact remains that people who store genomic data in repositories in healthcare settings are vulnerable to such breaches.

Beyond just the potential breach of security due to the technologies used, the collection and reuse of genomic data over time creates a number of privacy issues. Many pharmacogenomic databases contain an individual's genomic data in some form or another and retain it indefinitely for ongoing research and the development/training of models. As a result, this increases the risk of misuse or unauthorized access to an individual's genomic data. The international exchange of genomic data creates additional complexities around governance. Genomic data is exchanged across borders; therefore, different legal systems create different levels of protections for genomic data. There are challenges to obtaining valid informed consent from patients regarding AI-assisted pharmacogenomics. For example, patients may not completely comprehend how their genomic data will be utilized, particularly if they are consenting to utilize secondarily derived data, engage in federated learning, etc., continually train their models using patient genomic data [68] [24]. Dynamic consent frameworks have been suggested, enabling individuals to manage data sharing choices as time progresses; yet, their application stays restricted [8], [25]. Additionally, fair access to pharmacogenomic testing necessitates guarantees that data-sharing systems do not take advantage of marginalized groups or reinforce data colonialism.

7.2 Ethical Dilemmas

AI-based pharmacogenomics creates an ethical dilemma where a person's right to obtain individualized treatment conflicts with the use of algorithms in making treatment decisions. A primary issue associated with this conflict is that there exists a possibility for clinicians to rely too heavily on computer-generated recommendations (i.e., based on AI) as opposed to consulting other forms of data (e.g. from patients, family members etc.) regarding their patient's condition [77],[13].The "blackbox" characteristic of certain models brings up concerns of epistemic opacity, eroding confidence in systems whose reasoning behind decisions is not transparent to both patients and practitioners [24].

Another major ethics issue surrounding AI use in clinical settings, is accountability. As AI influence clinical decision-making, accountability issues arise with respect to the clinician, the organization, or the developer of the algorithm when errors occur. This ambiguity complicates the structure of liability and increases concerns regarding patient safety and liability.

One of the biggest ethics challenges facing AI development is algorithmic bias. An AI model is only as effective as its training data; therefore, if its training data does not reflect all possible patients (for example, only reflects European populations or only represents high-income healthcare systems) than the model will continue to support health disparities, and provide suboptimal care recommendations to minority populations [76], [11]. Additionally, pharmacogenomics presents a further layer of complexity because there are significant differences in allele frequencies across different ethnic and ancestral groups. To assist with genomic data stewardship, two frameworks that have been proposed include the FAIR Framework (findability, accessibility, interoperability and reuse), and the CARE Framework (collective benefit, authority to control, responsibility and ethics); however, both are currently inconsistent in adoption [8].

There also is growing concern about the potential for algorithmic determinism; whereby AI-generated predictions may dominate clinical decision making or patient autonomy. Therefore, it is essential to ensure that AI is used solely as a clinical decision support tool and not as a clinical decision maker to maintain ethics within the realm of clinical practice.

7.3 Regulatory Compliance

The landscape of regulations regarding AI in pharmacogenomics is currently fragmented and evolving. In the United States, software applications offering clinical decision support utilizing pharmacogenomic data could fall under FDA regulation as Software as a Medical Device (SaMD) [69]. However, there remains ambiguity surrounding the classification of AI models that continuously learn from live data, leading to uncertainties in approval and regulatory requirements [24].Although the U.S. FDA has issued "good machine learning practice" (GMLP) discussion papers that promote transparency in AI development, human oversight of risk, and ongoing human evaluation/monitoring of its operation - there have been no AI-specific federal regulations established.

Regulatory oversight involves much more than just obtaining final approval; once a product is deployed, regulators will also monitor how well the product operates. Adaptive AI systems will require continuous validation as they may deteriorate over time. Validation will need to be performed at multiple points during the life cycle of the system. Therefore, although a system may receive full or conditional approval when first deployed, it will likely not satisfy all regulatory requirements for its entire life cycle.

There are additional international regulatory complexities related to this topic. For example, the European Union has recently approved an Artificial Intelligence Act, and a General Data Protection Regulation (GDPR). A tiered regulatory framework is recommended as part of the AI Act, which would require that health related algorithm developers provide adequate documentation (e.g., data collection methods, assumptions made in programming), implement practices or mechanisms to reduce biases and monitor these systems continuously post-release [68].

In addition to providing clarity around their decision making processes, pharmacogenomic AI tool developers are obligated to ensure that their products adhere to clinical guidelines developed by organizations such as CPIC and/or local regulatory agencies, so as to ensure they can be safely applied ethically within practice [23].

In addition to issues of governance at a national level, another important emerging regulatory issue is that there are significant differences in governance frameworks among different countries; as such, these differences create barriers to deploying AI-based pharmacogenomic tools into global healthcare systems, emphasizing an urgent need for international standards governing their use. Table IV highlights important ethical and legal concerns in AI-based pharmacogenomics.

Ethical Dilemmas

Table IV: Summary of Key Ethical and Legal Issues in AI-Driven Pharmacogenomics

Domain	Representative Challenges
Privacy	Re-identification risk, lack of genomic data ownership laws, familial implications
Consent	Informed consent for AI use, secondary data use, dynamic consent gaps
Bias	Underrepresentation of populations, algorithmic inequities, fairness auditing
Governance	Lack of AI-specific regulation, uncertain FDA/EMA oversight for adaptive models

These ethical and legal factors highlight the necessity of creating strong governance structures that harmonize innovation with patient safety, privacy, and fairness. If these challenges are not addressed, the broad clinical implementation of AI-driven pharmacogenomics could be notably impeded.

8. FUTURE DIRECTIONS

8.1 Emerging Technologies

Advances in secure computing (e.g., federated learning) and advances in both AI architecture and data generation are expected to speed the use of pharmacogenomics in a clinical setting. Federated learning—decentralized machine learning—is one such advance that will allow models to be trained on top of data from many different organizations, thereby eliminating direct data sharing and therefore protecting the privacy of patients. By using this type of model with diverse datasets, it will also provide an opportunity to eliminate bias in pharmacogenomic AI models; early prototype applications have provided evidence of successful updates of secure models across large health care networks while maintaining confidentiality of all patient information [69] [24]; [23].

Advances in synthetic data production – including Generative Adversarial Networks (GANs), Variational Autoencoder (VAE)s -- are also being explored as potential means to supplement pharmacogenomic data sets that are too small. The synthetic data

produced by these methods will be a realistic representation of the distribution of genomic and clinical data found in real-world studies, thus potentially allowing researchers to mitigate some of the limitations associated with lack of sufficient numbers of subjects and/or class imbalance. The synthesis method may also provide the researcher an opportunity to ensure that their research remains private.

Transformers and Large Language Models (LLMs), e.g., BioGPT and Med-PaLM, are being developed that demonstrate the ability to process both unstructured and structured biomedical literature, as well as unstructured electronic health record (EHR) data; they have been shown to identify pharmacogenomic relationships [77][25] from this literature. Models such as these have been especially helpful in NLP applications such as extraction of gene-drug interactions in clinical note content, etc. and from published pharmacogenomics guidelines [69] – as well as in developing and implementing clinical decision support tools and systems to assist clinicians in reasoning through complex information (i.e., generation of patient-specific pharmacogenomics summaries; creation of explainable recommendations for patient treatments).

In addition, researchers are exploring the use of multimodal AI architectures which will be able to integrate genomic, transcriptomic, proteomic, and metabolomic data with longitudinal medical histories to develop higher-resolution and more accurate predictive models of optimal therapies for individual patients [68], [13]. The final purpose of this study is to provide for patients with an ongoing stream of data about their current status and how they are responding to treatment in real-time as opposed to providing one time static prediction. Further, using wearable devices and digital biomarkers could enhance these models through the addition of actual physiological and behavioral data.

8.2 Interdisciplinary Collaboration

The success of applying artificial intelligence in pharmacogenomics will depend upon effective partnerships across various disciplines, including bioinformatics, clinical pharmacology, computer science, ethics and regulatory science. To help ensure that machine learning (ML) models are based on a mechanistic understanding of how drugs are metabolized rather than solely on statistical correlation, pharmacologists need to work closely with data scientists [10], [11] . Ensuring that AI tools are both biologically understandable and align with standard care protocols requires collaborative relationships such as those shown by CPIC (Clinical Pharmacogenetics Implementation Consortium), PharmGKB and eMERGE who have provided examples of the successful use of a shared resource and standardized reporting to advance pharmacogenetic implementation [8], [64]. In the future, it is expected that these collaborations will include AI system developers, patient advocacy groups and policymakers to address the societal/ethical issues related to fair access to algorithms, transparencies regarding how algorithms function, and the development of policies governing the use of AI systems [24].

To allow comparison of AI model performance in differing studies, additional steps will need to occur. Development of benchmarking datasets and standardized assessments for evaluating AI models will provide necessary mechanisms for measuring the relative performances of AI models used within multiple studies. Establishing programs or standards similar to CONSORT-AI and TRIPOD-AI will assist in establishing an environment where researchers are able to transparently describe the design, testing and implementation of AI systems; ultimately providing an opportunity for increased levels of study replicability and validity when using pharmacogenomic-based AI systems to assess patient risk or identify patients who may benefit from a specific medication.

The education / training for clinicians, pharmacists, and genetic counselors needs to be developed to increase their ability to understand how AI works. With increased understanding of AI (AI literacy), these professionals can better understand how to use the output from AI models that are being used in pharmacogenomics and make patients more active participants in the decision making process. As well, there is a need for interdisciplinary education and/or training opportunities to close the gap between pharmacogenomics research and application through Data Science and Clinical Informatic.

8.3 Long-Term Goals

A key aim for the future is to develop real-time decision support using artificial intelligence (AI) at the bedside that can use pharmacogenomic information when caring for patients. To achieve this, these systems will need to seamlessly interface with electronic health records (EHRs), utilize clinically valid predictive modeling, and be able to learn as additional evidence becomes available. [69], [68] The expected AI systems will also allow for the ability to automatically make individualized dose adjustments, predict potential adverse events, and prevent drug-drug interactions. [67], [66]

A major part of achieving this vision is developing healthcare systems which continue to adapt through time; AI models can update themselves based upon real-world data and clinical outcome-based insights. These systems can facilitate the incorporation of new pharmacogenomic findings into clinical practices quickly, thus enhancing both safety and efficacy over time.

A longer term goal is to include pharmacogenomics within strategies for public health and population health monitoring. AI can help identify communities at higher risk for adverse medication reaction or treatment failure by identifying populations who may benefit from proactive testing and resource allocation [10], [23] This could result in improved cost-effectiveness of healthcare and better overall outcomes for all members of the population.

In the long run, making sure everyone has an equal opportunity to use AI-based pharmacogenomics will probably be one of the biggest hurdles for this area of research. Future systems need to be able to work with different kinds of people, minimize their biases and make sure that those who benefit from customized treatments get them fairly across all areas of health care. Digital Health (AI and Genomics) may allow for a time when every treatment decision is made based on someone's genetic makeup, their environment and how well the previous treatment worked — opening the door to a true age of completely individualized, proactive and fair health care.

9. CONCLUSION

AI and machine learning technologies are providing an accurate platform for applying artificial intelligence and machine learning to precision pharmacogenomics which is contributing to rapid advancement of personalized medicine. AI applications enable the combination of large amounts of genomic data, clinical information, and environmental variables using complex algorithms. The output from these AI platforms provides predictive insight into drugs that will have effectiveness on individual patients (enhanced efficacy) as well as minimize the likelihood of adverse effects (minimized risk). Ultimately, they can help make a decision about what treatment is most appropriate based on each patient's genetic profile. In several areas including oncology, cardiology and psychiatry, numerous real-world examples have been identified which illustrate how pharmacogenomics can be applied through use of AI algorithms to improve patient outcomes, as well as simplify clinical work flow processes [11], [69]. This review provides an overall view of what is currently being done with pharmacogenomics using artificial intelligence. The areas covered include the foundations for this area of research; the use of advanced machine learning methods to develop models and algorithms for the identification of genetic variants; the use of these developed models and algorithms in clinical applications; and the technical and practical challenges associated with implementing the results of this work into practice.

The integrated perspective provided by this review combines the views of those who study multiomics data analysis; those who are involved in the integration of electronic health records (EHR); and those who have expertise in developing clinical decision support systems (CDSS). Overall, this review provides an example of how pharmacology (computer-based technology) is being merged with computational intelligence.

The review further identifies the entire process for collecting data; developing models; and applying models clinically as significant advancement over previous reviews that treated each individually.

The new area of research has considerable potential but is encountering severe obstacles. The primary obstacles are data limitations, ambiguity surrounding the mechanisms of the algorithms, regulatory ambiguity and inequality. These issues can be resolved by providing standardized data infrastructure platforms.

For large-scale data collection and analysis; developing new explainable AI architectures; establishing international standards for regulatory approval of AI-based approaches; and fostering multidisciplinary collaboration among researchers, clinicians, and educators to promote both biological validity and clinical usefulness of new AI tools while ensuring their ethical implications are understood.

Successful collaborations demonstrate how interest groups focused on AI applications in medicine (e.g., CPIC, PharmGKB, eMERGE) can generate innovation opportunities, aid in the effective application of discoveries in clinical environments, and offer ongoing educational experiences for healthcare professionals [8], [64].

A major takeaway from this study is that there is currently no single artificial intelligence (AI) technique which can address the entire scope of pharmacogenetic prediction. Therefore, future clinical tools are expected to rely upon hybrid/multi-modal methods combining both structured and unstructured data and also incorporating expert domain knowledge.

To achieve broad acceptance in a clinical setting and build clinician confidence, the ability to provide interpretable and fair recommendations will be critical.

The use of Federated Learning, Large Language Models and Multimodal Data Fusion will transform how pharmacogenetics is used to make decisions at the bedside in real-time. Further enhancements to the precision and timeliness of pharmacogenetic therapies will occur as continued learning in healthcare systems evolves through the incorporation of real-world evidence and adaptive AI. However, to realize these benefits will require; the collection of a wide variety of genomic data, the education/training of clinicians regarding the use of AI-based pharmacogenetics, patient engagement/participation in AI-based pharmacogenetics, ongoing research, ethical oversight and policy alignment. Therefore, it appears that AI-based pharmacogenomics may finally allow us to accomplish the long-standing goal of having safe, equitable and personalized medical treatment.

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

Arwa Al Anber: oversight, ideation, approach, composition - initial draft creation.

Alaa t. Al ghazo: ideation, writing - initial draft creation.

Loiy Algazo: composing - initial draft creation.

Tasnim Masa'deh: composing - initial draft creation.

Wadea Megdadi: writing - original draft preparation.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

DATA AVAILABILITY STATEMENT

Data supporting the findings of this study are available from the corresponding author upon reasonable request.

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