

Artificial Intelligence and Multi-Omics in Pharmacogenomics: A New Era of Precision Medicine

Mike Zack, MD, PhD, MPH; Danil N. Stupichev, MSc; Alex J. Moore, BSc; Ioan D. Slobodchikov, MSc; David G. Sokolov, MSc; Igor F. Trifonov, MSc; and Allan Gobbs, MSc

Abstract

Pharmacogenomics is entering a transformative phase as high-throughput “omics” techniques become increasingly integrated with state-of-the-art artificial intelligence (AI) methods. Although early successes in single-gene pharmacogenetics reported clear clinical benefits, many drug response phenotypes are governed by intricate networks of genomic variants, epigenetic modifications, and metabolic pathways. Multi-omics approaches address this complexity by capturing genomic, transcriptomic, proteomic, and metabolomic data layers, offering a comprehensive view of patient-specific biology. Advanced AI models, including deep neural networks, graph neural networks, and representation learning techniques, further enhance this landscape by detecting hidden patterns, filling gaps in incomplete data sets, and enabling in silico simulations of treatment responses. Such capabilities not only improve predictive accuracy but also deepen mechanistic insights, revealing how gene–gene and gene–environment interactions shape therapeutic outcomes. At the same time, real-world data from diverse patient populations is broadening the evidence base, underscoring the importance of inclusive datasets and population-specific algorithms to reduce health disparities. Despite challenges related to data harmonization, interpretability, and regulatory oversight, the synergy between multi-omics integration and AI-driven analytics holds relevant promise for revolutionizing clinical decision-making. In this review, we highlighted key technological advances, discussed current limitations, and outlined future directions for translating multi-omics plus AI innovations into routine personalized medicine.

© 2025 THE AUTHORS. Published by Elsevier Inc on behalf of Mayo Foundation for Medical Education and Research. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>) ■ Mayo Clin Proc Digital Health 2025;3(3):100246

Pharmacogenetics, the study of how genetic variation influences drug response, emerged in the mid-20th century, when it was first recognized that inherited factors underlie individual differences in drug effects.¹ Landmark discoveries of allelic variants in drug-metabolizing enzymes, such as cytochrome P450 variants, found that genotyping could predict drug efficacy and toxicity, laying the groundwork for personalized medicine.² Genotype-guided prescribing, such as human leukocyte antigen allele screening or testing for enzyme variants, has reported tangible clinical benefits.

However, most early pharmacogenetic applications focused on one or a few genes, which proved insufficient for complex phenotypes driven by polygenic interactions and environmental factors.^{3,4} This realization prompted a shift from candidate-gene studies to genome-wide approaches (genome-wide association studies and next-generation sequencing). This process subsequently evolved into broader multi-omics strategies—integrating transcriptomic, proteomic, epigenomic, and metabolomic data to better capture the full biological context. For example, adding gene expression profiles to genomic variants improved warfarin dose

From the PGxAI Inc., Palo Alto, CA.

ARTICLE HIGHLIGHTS

- Multi-omics integration enables a more complete understanding of drug response beyond single-gene analysis.
- Advanced artificial intelligence methods, including graph neural networks, variational autoencoders, and large language models, enhance drug response prediction and clinical decision support.
- Real-world data enrich artificial models and support prospective validation in clinical settings.
- Barriers such as data complexity, equity, and clinician interpretability must be addressed to achieve clinical implementation.

prediction by 8%-12% in explained variance.¹

Challenges in Pharmacogenomics and the Promise of Artificial Intelligence-Powered Multi-Omics

Despite decades of progress, variability in drug response remains a major clinical challenge. Many patients experience suboptimal outcomes: some derive little therapeutic benefit, and others suffer serious adverse effects. Adverse drug reactions are estimated to be among the leading causes of mortality globally,^{5–8} although treatment failure is common in conditions like depression, cancer, and cardiovascular disease.^{9–12} Approximately 95% of individuals carry at least 1 actionable pharmacogenomic variant,^{1,13,14} yet existing tools still fail to consistently predict drug response.

A key limitation is that traditional pharmacogenomics (PGx) often relies on static germline variants, ignoring downstream regulatory effects and context-dependent biology.¹⁵ Many pharmacogenomic phenotypes are polygenic, dynamic, and modulated by epigenetics, gene expression, protein levels, and metabolic context.^{3,16,17} For example, DNA methylation patterns can influence antidepressant outcomes independently of genotype,^{18,19} and proteomic or metabolomic variation can markedly alter drug absorption, metabolism, and efficacy.

This has led to growing interest in multi-omics frameworks, which integrate diverse molecular layers to model drug response

more comprehensively.^{1,20} At the same time, advances in artificial intelligence (AI), particularly deep learning and generative models, now offer powerful tools for integrating high-dimensional multi-omics data, uncovering latent biological patterns, and enabling patient-specific prediction.^{20–22}

Objective of This Review

This review provides a comprehensive overview of current strategies combining multi-omics and AI in PGx. We highlighted recent methodological advances, assessed their potential to improve predictive performance, and discussed key challenges in translating these tools into clinical practice. We aimed to show how this integrative paradigm is reshaping precision medicine by bringing us closer to matching each patient with the right drug at the right dose.

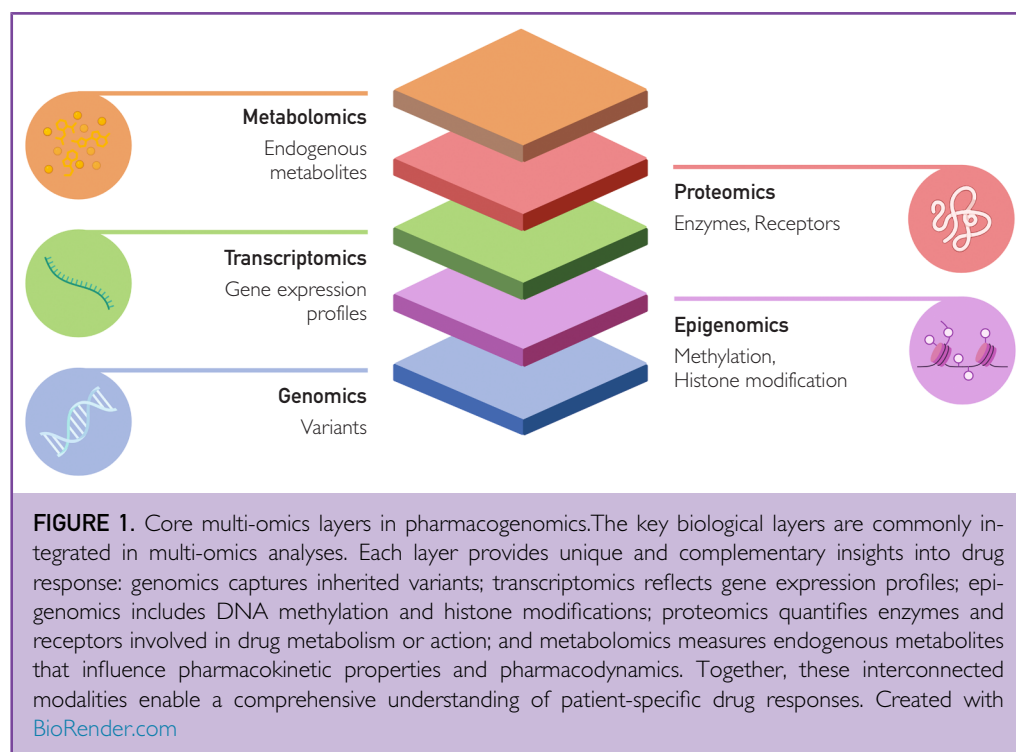
MULTI-OMICS APPROACH IN PERSONALIZED MEDICINE

Definition and Rationale

Multi-omics refers to the integrative analysis of two or more biological layers to generate a comprehensive molecular portrait of biological systems, typically including genomics and transcriptomics, and increasingly incorporating epigenomics, proteomics, and metabolomics (Figure 1).^{23,24} It recognizes that genotype alone does not capture dynamic processes such as gene regulation, post-translational modifications, or shifts in metabolism. Each “omic” dimension offers distinct insights: genomic variants predict potential risk or capacity for drug metabolism, whereas transcriptomic and proteomic profiles indicate actual activity states of genes and proteins.²⁴

Interdisciplinary Nature and Data Complexity

Multi-omics merges diverse data types: DNA variant calls, RNA expression matrices, methylation profiles, proteomic readouts, metabolite concentrations, and sometimes 16S ribosomal RNA or metagenomic data.^{24,25} Each platform has unique noise features and measurement biases, requiring specialized bioinformatic pipelines.²³ Data scientists, statisticians, molecular biologists,



and clinicians must collaborate to ensure these heterogeneous layers are processed and interpreted properly.²⁵

Advantages Over Single-Layer Analyses

Integrating multiple layers often reveals relationships invisible to siloed approaches. For example, linking a genetic variant to changes in gene expression and subsequent protein activity can clarify causal mechanisms and reduce false positives.²⁶ Multi-omics modeling also tends to be more accurate for predicting clinical outcomes, as it exploits the regulatory cascades connecting different omic layers.^{27,28} Studies in oncology, cardiology, and endocrine disorders have shown that multi-omic signatures provide refined patient stratification and better prediction of drug response than a single-layer alone.^{25–27,29}

Big Data Challenges

Although powerful, multi-omics faces standard “big data” hurdles, including high dimensionality, missing values, and batch effects. Combining data from multiple platforms can introduce systematic biases if not

properly corrected.³⁰ Moreover, each omics modality brings additional data complexity, forcing researchers to apply robust normalization and integration methods.^{24,30} If sample sizes are small relative to the number of features, overfitting becomes a concern. Nevertheless, methodological advances, including deep learning and Bayesian frameworks, are increasingly able to extract meaningful patterns from multi-modal data.^{23,31}

Existing Integration Approaches

Classical methods such as canonical correlation analysis or joint factorization have a long-standing history in multi-omics integration.²⁶ More recent AI-driven methods (including variational autoencoders and graph neural networks) can capture complex, nonlinear structures among omics layers and mitigate issues like missing data.^{24,25}

Real-World Applications

Oncology was an early adopter, as large initiatives like the Cancer Genome Atlas integrated genomic, epigenomic, and transcriptomic data to redefine tumor subtypes and discover

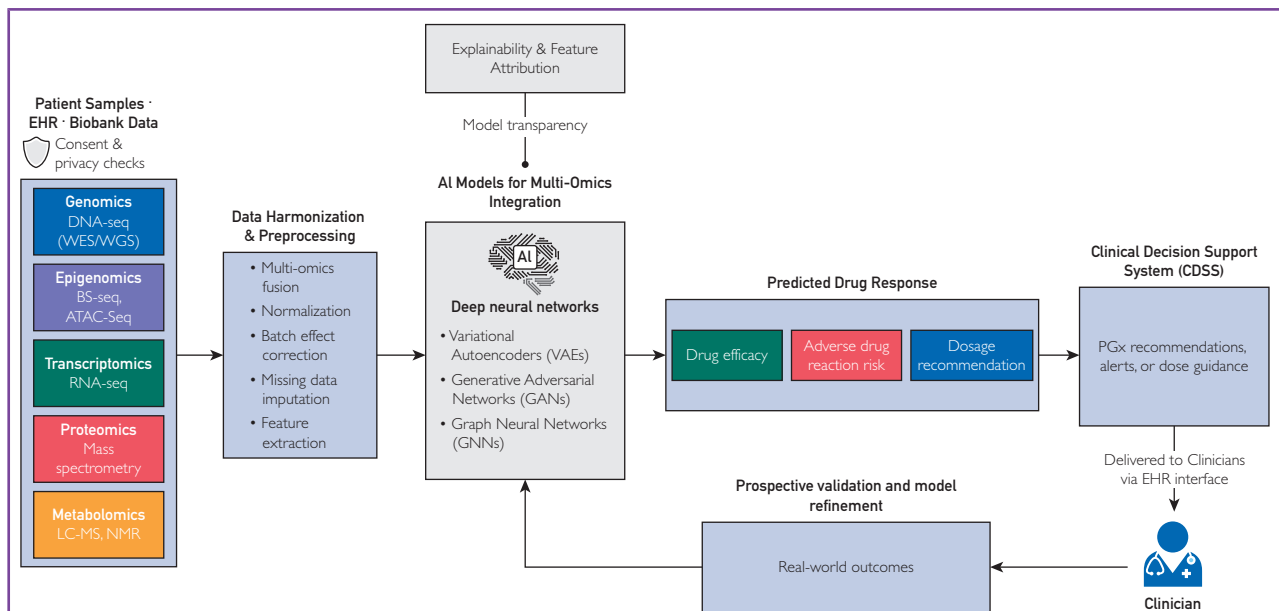


FIGURE 2. Artificial intelligence (AI)-powered multi-omics pipeline for predicting drug response. Patient-derived omics data, including genomics (eg, whole exome sequencing [WES]/whole genome sequencing [WGS]), epigenomics (eg, bisulfite sequencing [BS-seq], assay for transposase-accessible chromatin using sequencing [ATAC-seq]), transcriptomics (RNA-seq), proteomics (mass spectrometry), and metabolomics (eg, Liquid chromatography-mass spectrometry [LC-MS], nuclear magnetic resonance [NMR]), are fused and harmonized for model input. Deep learning models (eg, variational autoencoders [VAEs], generative adversarial networks [GANs], [GNNs]) predict drug efficacy, adverse drug reaction (ADR) risk, and dosage recommendations. Explainability modules enhance model transparency, while validation on real-world outcomes enables continuous refinement. Final outputs are delivered to clinicians via clinical decision support systems (CDSS) integrated into the electronic health record (her). Created with BioRender.com.

new biomarkers.²⁶ In cardiology, multi-omics has led to improved risk stratification for atherosclerosis.²⁷ In endocrinology, it helps explain why 2 patients with similar genetic variants show different responses to the same therapy; factors like epigenetics or proteomics can account for unexplained variability.²⁵ Such examples demonstrate multi-omics' capacity to illuminate complex biological systems and enable a more nuanced approach to personalized medicine.

AI for Multi-Omics Integration

The integration of multi-omics data, spanning genomics, transcriptomics, epigenomics, proteomics, and metabolomics, has enabled a more comprehensive understanding of drug response. However, the high dimensionality, missing modalities, and complex biological relationships between these data layers present unique analytical challenges. Deep

learning models offer powerful tools to address this complexity by extracting latent patterns and predicting clinical outcomes such as drug efficacy, adverse drug reactions, and optimal dosage.

Figure 2 illustrates a typical AI-powered multi-omics workflow. After harmonization steps (eg, normalization, batch correction, and imputation), data are processed by deep neural networks, including variational autoencoders, generative adversarial networks, and graph neural networks. These architectures allow integration of heterogeneous data types and enable simulations of treatment scenarios. Importantly, explainability modules help clinicians interpret predictions, and validation on real-world outcome data (eg, electronic health record [EHR]-linked cohorts) supports prospective refinement.

Recently, multiple studies have found that integrating multi-omics with AI improves

TABLE. Artificial Intelligence (AI)-Based Models for Multi-Omics Integration in Pharmacogenomics (2018-2025)					
Method name	Reference, year	Omics layers	AI method	Use case	Outcome
DeepDRA	Mohammadzadeh-Vardin et al, ³³ 2024	Genomics, transcriptomics, and drug structure	Autoencoders + MLP	Cancer drug sensitivity	AUPRC values 0.99 (internal) and 0.72 (external)
Multi-omics predictor of antidepressant response	Joyce et al, ³⁴ 2021	Genotyping and metabolomics	Logistic regression	Antidepressant response	AUC values increased from 0.84-0.86
MOICVAE	Wang et al, ³⁵ 2023	Genomics (sequence variation and CNV), and transcriptomics	Variational autoencoder	Pan-cancer drug sensitivity	AUC values up to 0.91 on TCGA
Dr.VAE	Rampášek et al, ³⁶ 2019	Transcriptomics and drug perturbation	Variational autoencoder	Cancer drug sensitivity	Outperformed standard ML on 23 of 26 drugs
MOVIDA	Ferraro et al, ³⁷ 2023	Transcriptomics and sequence variation + drug descriptors	Visible neural network	Cancer drug sensitivity	Better accuracy in imbalanced data
MOFGCN	Peng et al, ³⁸ 2022	Multi-omics + drug graphs	Graph convolutional network	Drug sensitivity prediction	Improved prediction vs other methods
TSGCNN	Peng et al, ³² 2023	Multi-omics + drug graphs	Two-space graph CNN	Cancer drug response	Outperformed 8 SOTA methods
NDSP	Liu and Mei, ³¹ 2023	Transcriptomics, CNV, and methylation	Sparse PCA + DNN	Drug sensitivity (GDSC)	Better prediction for all drug classes
MOLI	Sharifi-Noghabi et al, ³⁹ 2019	Genomics (sequence variation and CNV) and transcriptomics	Triplet-loss DNN	Prostate cancer drug response	Higher AUC value than single-omics
DL+ multi-omics in cancer	Wang et al, ⁴⁰ 2022	Transcriptomics, genomics, proteomics, and metabolomics	Graph embedding + attention	Drug IC50 prediction	R ² ~0.90
Super.FELT	Park et al, ⁴¹ 2021	Transcriptomics, sequence variation, and CNV	Triplet-loss autoencoder + classifier	Drug sensitivity/resistance	Best performance on patient data
Breast cancer therapy response	Sammut et al, ⁴² 2022	Genomics, transcriptomics, and pathology + clinical	Ensemble ML	pCR prediction	AUC value = 0.87
Each entry includes omics layers used, model type, clinical context, and quantitative improvements over baseline methods. All studies are indexed in PubMed and involve original experimental datasets.					
As the field progresses, combining deep learning with explainable frameworks, federated data sharing, and diverse population cohorts will be essential for translating these models into equitable, generalizable clinical tools.					
AUC, area under the curve; AUPRC, area under the precision-recall curve; CNN, convolutional neural network; CNV, copy number variation; DNN, deep neural network; GDSC, genomics of drug sensitivity in cancer; IC50, inhibitory concentration 50%; ML, machine learning; MLP, multi-layer perceptron; PCA, principal component analysis; pCR, pathologic complete response; SOTA, self-organizing tree algorithm; TCGA, the cancer genomic atlas.					

model performance across various pharmacogenomic applications. Table^{31–42} summarizes key original publications from 2018-2025, highlighting improved prediction of drug sensitivity, toxicity, and treatment response compared with single-omics or traditional methods. For instance, DeepDRA (2024) achieved a precision-recall area under the curve (AUC) value of 0.99 in drug response

prediction using autoencoders on transcriptomic and genomic data, while MOVIDA (2023) combined multi-omics with biologically informed architectures to enhance interpretability and outperform previous machine learning (ML) baselines. Similarly, MOICVAE (2023) and TSGCNN (2023) used graph-based and variational models to improve pan-cancer drug sensitivity prediction.^{32,43}

These examples demonstrate the growing maturity of generative and graph-based models for multi-modal learning. Across use cases, from chemotherapy toxicity to immunotherapy response, AI-driven integration consistently yields 5%-20% gains in predictive accuracy or AUC value.

AI for Real-World Pharmacogenomics

The integration of multi-omics data with AI is increasingly moving from research settings into real-world clinical practice. Retrospective analyses of outcome-linked omics datasets have reported that ML can uncover drug resistance mechanisms and stratify patients by likely therapeutic response. For instance, a multi-omics study of 400 patients with cancer identified subgroups with estrogen-dependent vs resistant tumors after cyclin-dependent kinase 4 and 6 inhibitors treatment, with ML results confirmed using experimental assays.²⁹ Natural language processing of EHRs has also been used to improve phenotype extraction and refine AI models for psychiatric PGx.⁴⁴

Real-world pharmacogenomic applications already show measurable clinical benefits. For example, pre-treatment dihydropyrimidine dehydrogenase (DPYD) genotyping in patients receiving fluoropyrimidines has nearly eliminated severe 5-fluorouracil toxicity in routine oncology, reducing hospitalization rates and preventing treatment-related deaths.^{45,46} The 100,000 Genomes Project further validated that carriers of DPYD variants are at considerably higher risk of chemotherapy-induced adverse events, supporting genotype-guided dose modifications.⁴⁷ See Box 1 for a real-world case illustrating DPYD-guided dosing.⁴⁸

Similarly, CYP2C19 loss-of-function alleles have been linked to increased cardiovascular events in clopidogrel-treated patients, prompting real-world guideline shifts toward alternative antiplatelet therapy.^{49,50} In anticoagulation, genotype-guided warfarin dosing has led to faster time-to-INR stabilization and fewer complications.^{51,52} Broader use of multi-gene PGx panels has reduced serious adverse drug reactions and hospitalizations across multiple specialties.^{45,53} As more clinical cohorts are subjected to multi-omics profiling, AI-based systems trained on these

real-world data (RWD) are likely to inform prospective therapeutic decisions, closing the loop between data generation and bedside application.

Box 1. CLINICAL VIGNETTE: MISSED HAPB3 VARIANT LEADS TO SEVERE FLUOROPYRIMIDINE TOXICITY

A 48-year-old woman with stage III rectosigmoid adenocarcinoma developed severe toxicity during adjuvant capecitabine/oxaliplatin therapy, including grade 3 gastrointestinal symptoms and febrile neutropenia, requiring hospitalization.⁴⁸ A commercial DPYD test returned a false-negative result, but follow-up testing with an expanded in-house panel revealed a heterozygous c.1236G>A (HapB3) variant associated with reduced dihydropyrimidine dehydrogenase activity. After dose adjustment, the patient tolerated chemotherapy well. This case highlights the clinical importance of comprehensive DPYD variant detection to prevent adverse outcomes.

Emerging Role of LLMs

In addition to deep learning architectures like autoencoders and graph neural networks, large language models (LLMs) are emerging as powerful tools in PGx. A recent study demonstrated that a generative pre-trained transformer 4-4-based assistant using retrieval-augmented generation outperformed general-purpose models when answering PGx-specific queries, showing the utility of domain-informed LLMs for clinical decision support.⁵⁴ Complementary to this, PGxQA was developed as a benchmark framework to evaluate LLM performance in PGx tasks across clinician, patient, and researcher perspectives, highlighting both rapid progress and ongoing risks in clinical deployment.⁵⁵ Together, these studies suggest that LLMs, although still maturing, could play a key role in improving PGx literacy and accessibility.

Barriers to Implementation of AI-Driven Multi-Omics in Clinical Practice

Despite the transformative promise of multi-omics and AI in precision medicine, several

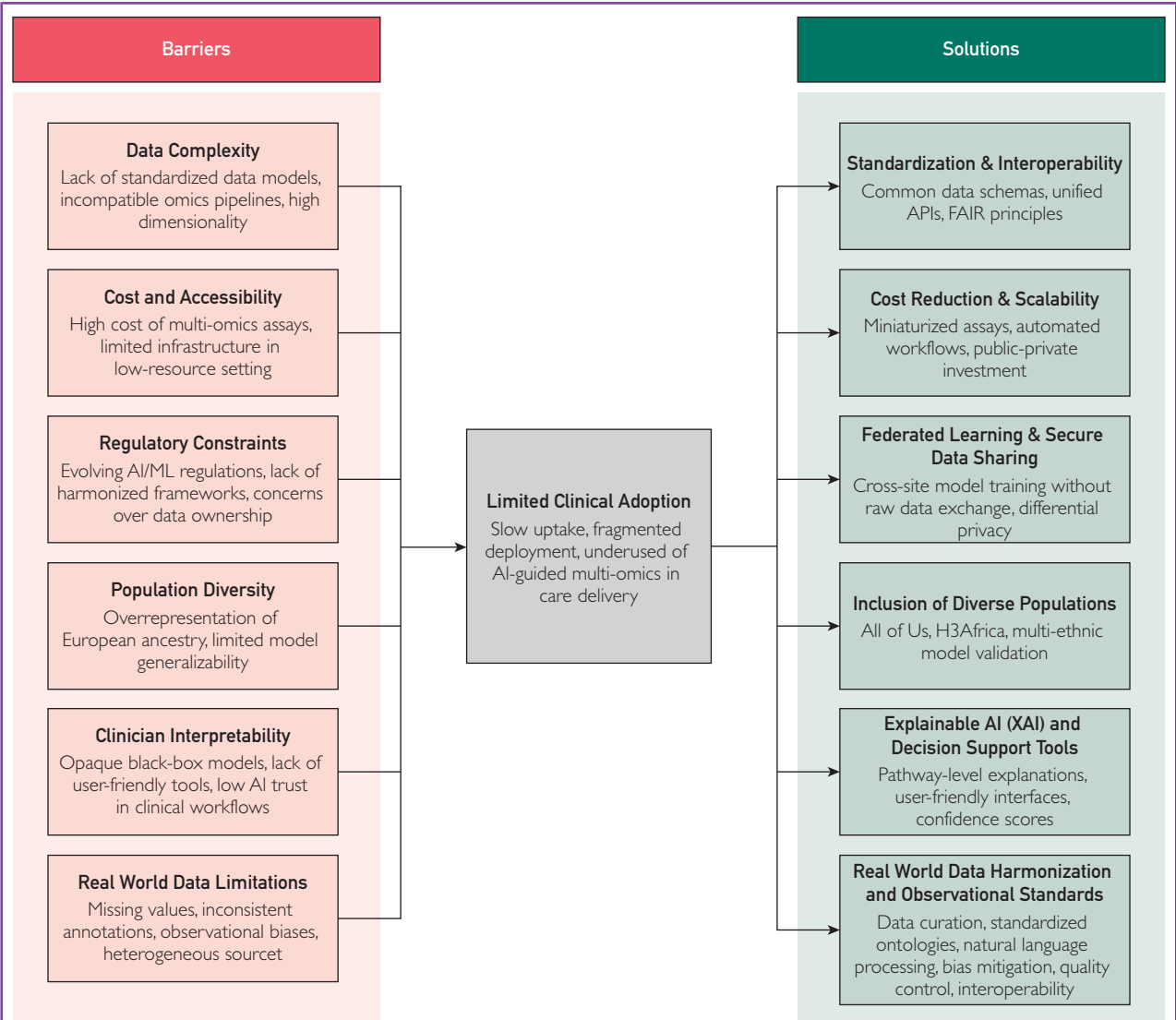


FIGURE 3. Barriers and solutions for implementing artificial intelligence (AI)-powered multi-omics in clinical practice. Key obstacles hindering the clinical adoption of multi-omics and AI technologies include data complexity, high costs, regulatory challenges, limited population diversity, and the low interpretability of AI models. Each barrier contributes to the limited use of AI-guided multi-omics in routine care. On the right, corresponding solutions are proposed, ranging from standardization and cost reduction to federated learning, inclusive data practices, and explainable AI tools, to promote broader, equitable, and sustainable integration into health care systems. Created with [BioRender.com](https://www.biorender.com)

critical barriers currently limit their widespread adoption in clinical settings. These obstacles span technical, infrastructural, regulatory, and human factors, each impeding the translation of high-dimensional multi-modal data into actionable clinical insights (Figure 3).

Data Complexity. Multi-omics data are inherently heterogeneous and high-dimensional, combining distinct data types, such as DNA variants, RNA expression levels, protein abundances, and metabolites, each with unique scales, noise characteristics, and formats. The integration of these data requires

sophisticated bioinformatics workflows capable of preserving biological context across layers. However, there is currently a lack of standardized data models and metadata schemas, as well as incompatible processing pipelines across omics domains, complicating interoperability and reproducibility.^{23,24}

Batch effects, missing modalities, and non-uniform data acquisition protocols are additional obstacles that demand careful normalization and correction strategies. Without rigorous standardization, integrating multi-omics data from different institutions or platforms risks introducing bias and undermining model validity.³⁰

Real-World Data Limitations. RWD, including EHRs, biobanks, and registry-linked omics, holds great promise for scaling AI-driven PGx. However, these datasets often suffer from missing values, inconsistent clinical annotations, and heterogeneity across institutions. Observational designs also introduce confounders and selection biases, as patients are not randomized, and certain populations may be underrepresented, potentially skewing results.⁵⁶ Harmonizing omics and clinical data across health care systems is further complicated by incompatible coding standards, differing assay platforms, and variable data quality.⁴⁴

Standardization efforts, such as adopting common ontologies and applying natural language processing to unstructured notes, are underway, but integrating large-scale, high-quality RWD into clinical-grade AI models remains a major challenge. Achieving this will require robust pipelines for data curation, interoperability, and quality control to ensure that pharmacogenomic insights derived from RWD are accurate, generalizable, and ethically implemented.

Cost and Accessibility. The generation and analysis of multi-omics data remain costly and resource-intensive. Although sequencing costs have decreased over time, comprehensive multi-omics profiling, including epigenomic, proteomic, and metabolomic layers, requires specialized infrastructure and expertise that are often unavailable in standard clinical laboratories. As a result, adoption has been largely restricted to research centers or

well-funded institutions, limiting equity and access.^{57,58}

In low-resource settings, this cost barrier is even more pronounced, perpetuating disparities in access to precision medicine. Further, implementing and maintaining AI models that operate on large-scale multi-modal data adds computational burden and infrastructure requirements beyond the reach of many health care providers.

Regulatory Constraints. Multi-omics data and AI-driven tools raise complex regulatory questions regarding algorithm validation, data interoperability, and post-market surveillance. Evolving legal frameworks, such as the EU's General Data Protection Regulation and the US Food and Drug Administration's evolving approach to software as a medical device, create uncertainty around adherence, especially in cross-border collaborations.⁵⁹

Additionally, there is no global consensus on how AI/ML algorithms used in clinical care should be regulated over their lifecycle, particularly if they are adaptive or continuously learning. Concerns about the liability and auditability of AI outputs remain unresolved and slow down implementation.⁶⁰ To improve transparency and oversight, regulators increasingly call for explainable models, version tracking, and real-world performance monitoring.

Ethical Considerations. As AI systems are increasingly deployed in pharmacogenomics, ethical concerns around patient consent, data ownership, and algorithmic bias become critical. Genomic and clinical data used to train AI models are often repurposed from biobanks or EHRs, raising questions about secondary use and transparency in consent processes.⁶¹ Moreover, data ownership remains ambiguous in many jurisdictions, particularly in commercial applications in which patient data may fuel proprietary models.⁶² Bias in training data can propagate inequities in AI outputs, especially when underrepresented populations are missing from training cohorts, leading to less accurate predictions and potentially harmful recommendations. Addressing these concerns requires proactive governance frameworks, representative datasets, and transparent AI

development practices to ensure equitable and trustworthy clinical implementation.

Population Diversity. Most AI models and omics datasets are derived from cohorts of European ancestry, resulting in poor generalizability to underrepresented populations. More than 80% of genomic data used in PGx and precision medicine originates from European or East Asian populations, while African, Latin American, and Indigenous groups remain severely underrepresented.^{63–65}

This imbalance introduces substantial bias into models and risks exacerbating health disparities if AI tools trained on non-representative data are applied universally.⁶⁶ For example, warfarin dosing models on the basis of European allele frequencies have led to incorrect dosing in patients of African ancestry, underscoring the need for population-specific algorithms and diverse reference datasets.⁶⁷

Global initiatives such as All of Us, PAGE, and H3Africa are actively working to diversify genomic datasets by recruiting underrepresented populations.^{62,63} Complementary strategies include population-specific model tuning, federated learning, and synthetic data generation, all aiming to improve fairness and generalizability of AI tools across ancestries.

Clinician Interpretability and Human Capital. The successful clinical use of AI-driven multi-omics tools depends on their acceptance and understanding by healthcare professionals. However, current models, particularly deep learning and generative architectures, often operate as opaque “black boxes,” making it difficult for clinicians to interpret or trust their outputs.⁶⁰

Further, most clinicians lack formal training in data science or omics analytics, creating a steep learning curve for the adoption of these tools. The absence of user-friendly interfaces and explainable outputs contributes to skepticism and low integration into clinical workflows, even when models demonstrate high predictive performance.²⁴

FUTURE OUTLOOK AND CONCLUSIONS

Clinical Impact to Date

AI-powered multi-omics integration has already found measurable benefits across

multiple medical domains. In oncology, algorithms trained on genomic, transcriptomic, proteomic, and imaging data can stratify tumors more precisely and identify patient-specific treatment options.^{68,69} One striking example is the Molecular Twin platform for pancreatic cancer, which combines tumor DNA/RNA, plasma proteomics, lipidomics, and digital pathology to predict survival and personalize therapy beyond traditional biomarkers like carbohydrate antigen 19-9.⁷⁰

In cardiology, AI models leveraging multi-omics biomarkers, especially combining genomic and proteomic data, outperform traditional risk scores in predicting myocardial infarction and other cardiovascular outcomes.⁷¹ In endocrinology, longitudinal profiling of individuals at risk for diabetes, incorporating multi-omics and wearable sensor data, revealed >60 actionable insights, including previously unknown pathways for metabolic dysfunction.⁷²

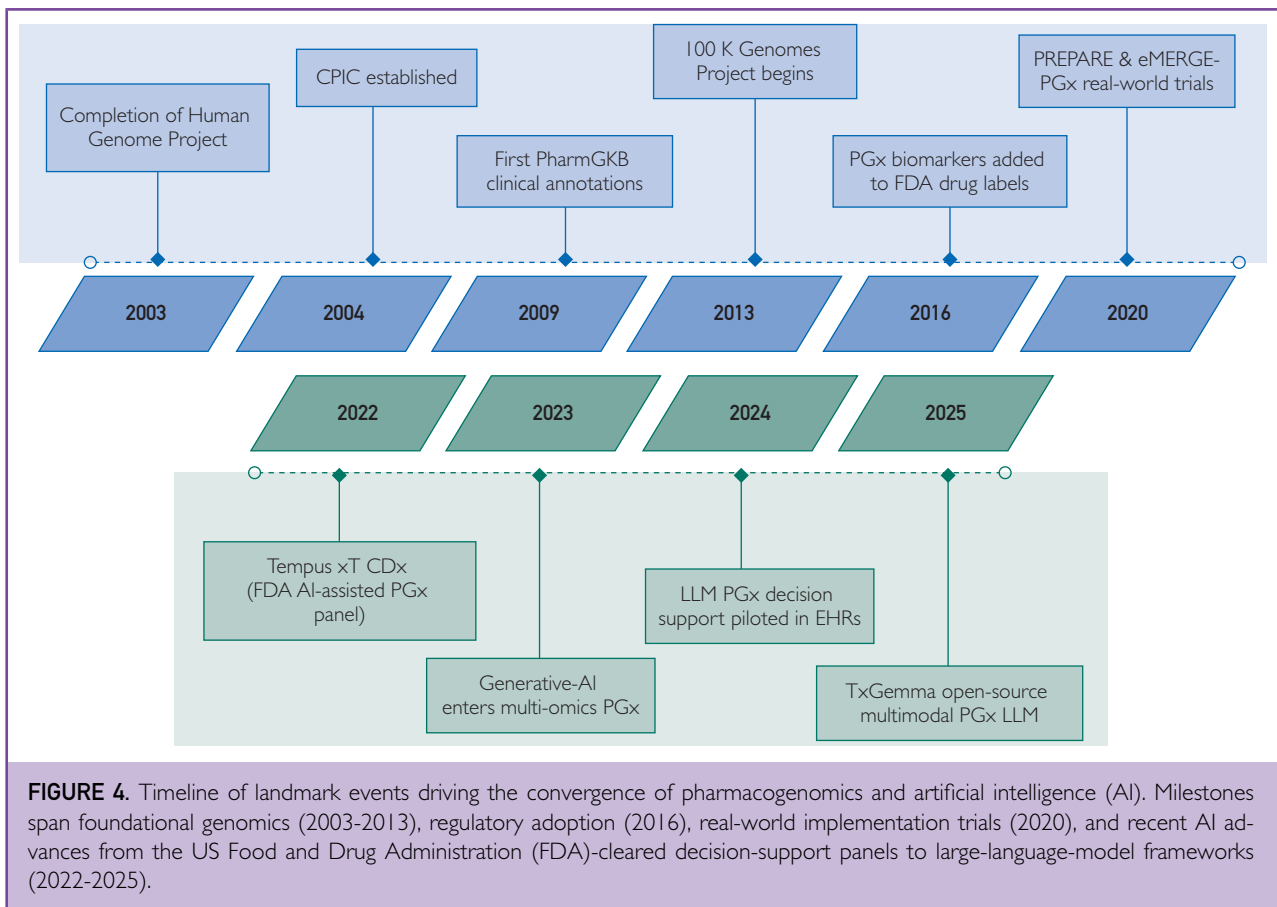
Psychiatry, long plagued by trial-and-error prescribing, is now seeing transformation through pharmaco-multiomics. Early studies have shown that combining genomic, epigenomic, and proteomic markers with clinical data improves prediction of antidepressant efficacy and side-effect risk,⁵⁸ laying the foundation for more personalized mental health interventions.

Over the past 2 decades, pharmacogenomics has evolved from foundational genomic initiatives (eg, the Human Genome Project, Clinical Pharmacogenetics Implementation Consortium guidelines) to large-scale clinical implementation trials (eg, PREPARE, eMERGE), culminating in recent AI-powered tools such as the Tempus xT CDx panel with integrated PGx reporting and open-access models like TxGemma for interpretable multi-modal prediction.⁷³ Figure 4 summarizes these milestones, charting the field's evolution toward AI-enabled precision medicine.

These examples signal that AI-driven multi-omics is not a distant vision. It is already refining diagnostics and treatment selection in real-world scenarios.

Emerging Innovations and Technological Trends

Several innovations are poised to mitigate these limitations and accelerate clinical translation:



- **Multi-Omics Foundation Models.** Inspired by large language models, researchers are building foundation models trained on vast, heterogeneous biomedical data (genomics, proteomics, EHRs, and imaging). These models can be fine-tuned for specific clinical tasks using much smaller datasets, improving accessibility and performance across domains.²⁰
- **Digital Twins.** Virtual patient replicas that integrate an individual's omics, clinical history, and sensor data enable *in silico* simulation of disease progression and therapy response. In oncology, these systems have been used to test thousands of drug options per patient, identifying optimal treatment strategies without risk of harm.⁷⁴ Beyond cancer, digital twins could support real-time disease monitoring and dynamic treatment adjustments in long-term conditions.
- **RWD as a Validation Infrastructure.** RWD is becoming a cornerstone for validating AI-driven multi-omics models in routine care. Unlike randomized clinical trials, RWD from EHRs, registries, and biobanks captures diverse patient populations, comorbidities, and medication usage patterns, enabling broader generalizability of pharmacogenomic insights.⁵⁶ These datasets help identify rare gene–drug interactions that may be missed in pre-approval studies and enable model training in realistic clinical contexts.⁴⁵ Integration of RWD into multi-omics pipelines also facilitates phenotype refinement using techniques like natural language processing of unstructured EHRs.⁴⁴ Together, these advances help close the gap between AI-driven prediction models and their clinical utility.

These technologies represent more than incremental advances, as they mark the transition from snapshot-based diagnostics to continuous, adaptive, and preemptive care.

Toward Predictive and Preventive Health Care

The most transformative impact of AI-powered multi-omics may lie in its ability to shift health care from reactive to predictive and preventive. Rather than waiting for symptoms to appear, clinicians will use molecular profiles and real-time data to forecast disease risk, intervene earlier, and tailor interventions with unmatched precision.

Future care pathways will increasingly rely on molecular stratification, not only determining who needs treatment but also identifying what mechanism underlies their condition. Two patients with the same diagnosis (eg, type 2 diabetes or heart failure) may receive entirely different treatments on the basis of whether their omics signatures point to immunologic, metabolic, or microbiomic drivers.

Over time, AI models trained on diverse, longitudinal multi-omics data will power real-time clinical decision-making: adjusting drug doses on the basis of wearable feedback, recommending diet changes informed by gut microbiome, or predicting sudden flare-ups from subtle molecular perturbations. Such systems will enable clinicians to maintain health, not just manage disease.⁷⁴

Key Priorities for the Next Decade

To bring this vision to life, the field must address the following priorities:

- External validation across diverse cohorts to ensure model robustness and fairness.⁵⁸
- User-centered tools that distill omics insights into clinically actionable guidance.²⁴
- Standardized data formats, application programming interfaces, and metadata schemas to facilitate cross-platform interoperability.
- Affordable, scalable assays for omics data generation in routine care.
- Inclusion of underrepresented populations in training datasets.⁶⁶

- Clear regulatory and ethical frameworks around privacy, transparency, and accountability.⁶¹

International efforts like Global Alliance for Genomics and Health and the All of Us program show how collaborative infrastructure can serve as a foundation for equitable and scalable precision health.

Final Perspective: Building the Future of Data-Driven Medicine

The convergence of AI, multi-omics, and real-world data analytics signals a profound shift in health care. With sustained global collaboration and thoughtful regulation, AI-powered multi-omics tools can become standard in diagnostics, therapy optimization, and lifelong health monitoring.

This transformation hinges not just on algorithms or datasets but on interdisciplinary collaboration, bringing together scientists, clinicians, engineers, ethicists, and patients. If key challenges in equity, interoperability, and clinical usability are addressed, the next decade will witness a transition from precision medicine as a promise to precision medicine as a practice: universal, adaptive, and human-centered.

POTENTIAL COMPETING INTERESTS

All authors are employees of PGxAI Inc.

Abbreviations and Acronyms: AI, artificial intelligence; ADR, adverse drug reaction; EHR, electronic health record; LLM, large language model; ML, machine learning; PGx, pharmacogenomics; RWD, real-world data

Grant Support: This research was financed solely by the authors' funds. No external funding was received.

Correspondence: Address to Mike Zack, MD, PhD, MPH, PGxAI Inc., 330 E Charleston Rd, Palo Alto, CA 94306 (mz@pgx.ai).

ORCID

Mike Zack:  <https://orcid.org/0000-0002-3964-9726>;
Allan Gobbs:  <https://orcid.org/0009-0004-7657-9570>

REFERENCES

1. Auwerx C, Sadler MC, Reymond A, Kutalik Z. From pharmacogenetics to pharmaco-omics: milestones and future directions. *HGG Adv*. 2022;3(2):100100. <https://doi.org/10.1016/j.xhgg.2022.100100>

2. Weinshilboum RM, Wang L. Pharmacogenomics: precision medicine and drug response. *Mayo Clin Proc.* 2017;92(11):1711-1722. <https://doi.org/10.1016/j.mayocp.2017.09.001>
3. Simona A, Song W, Bates DW, Samer CF. Polygenic risk scores in pharmacogenomics: opportunities and challenges—a mini review. *Front Genet.* 2023;14:1217049. <https://doi.org/10.3389/fgene.2023.1217049>
4. Singh M, Kumar A, Khanna NN, et al. Artificial intelligence for cardiovascular disease risk assessment in personalised framework: a scoping review. *EClinicalMedicine.* 2024;73:102660. <https://doi.org/10.1016/j.eclinm.2024.102660>
5. Le Louët H, Pitts PJ. Twenty-first century global ADR management: a need for clarification, redesign, and coordinated action. *Ther Innov Regul Sci.* 2023;57(1):100-103. <https://doi.org/10.1007/s43441-022-00443-8>
6. Siddiqui MK, Luzum J, Coenen M, Mahmoudpour SH. Editorial: pharmacogenomics of adverse drug reactions. *Front Genet.* 2022;13:859909. <https://doi.org/10.3389/fgene.2022.859909>
7. Jordan IK, Sharma S, Mariño-Ramírez L. Population Pharmacogenomics for Health Equity. *Genes (Basel).* 2023;14(10):1840. <https://doi.org/10.3390/genes14101840> PMID: 37994414.
8. Santenna C, Shubham A, Ratinder J, et al. Drug metabolizing enzymes pharmacogenetic variation-informed antidepressant therapy approach for common mental disorders: a systematic review and meta-analysis. *J Affect Disord.* 2024;367:832-844. <https://doi.org/10.1016/j.jad.2024.09.041>
9. Mini E, Nobili S. Pharmacogenetics: implementing personalized medicine. *Clin Cases Miner Bone Metab.* 2009;6(1):17-24.
10. Pirmohamed M. Pharmacogenomics: current status and future perspectives. *Nat Rev Genet.* 2023;24(6):350-362. <https://doi.org/10.1038/s41576-022-00572-8>
11. Oslin DW, Lynch KG, Shih MC, et al. Effect of pharmacogenomic testing for drug-gene interactions on medication selection and remission of symptoms in major depressive disorder: the PRIME care randomized clinical trial. *JAMA.* 2022;328(2):151-161. <https://doi.org/10.1001/jama.2022.9805>
12. Li J, Li L, You P, Wei Y, Xu B. Towards artificial intelligence to multi-omics characterization of tumor heterogeneity in esophageal cancer. *Semin Cancer Biol.* 2023;91:35-49. <https://doi.org/10.1016/j.semcancer.2023.02.009>
13. Haidar CE, Crews KR, Hoffman JM, Relling MV, Caudle KE. Advancing Pharmacogenomics from single-gene to preemptive testing. *Annu Rev Genomics Hum Genet.* 2022;23:449-473. <https://doi.org/10.1146/annurev-genom-111621-102737>
14. Hodel F, De Min MB, Thorball CW, et al. Prevalence of actionable pharmacogenetic variants and high-risk drug prescriptions: a Swiss hospital-based cohort study. *Clin Transl Sci.* 2024;17(9):e70009. <https://doi.org/10.1111/cts.70009>
15. Alemu R, Sharew NT, Arsano YY, et al. Multi-omics approaches for understanding gene-environment interactions in noncommunicable diseases: techniques, translation, and equity issues. *Hum Genomics.* 2025;19(1):8. <https://doi.org/10.1186/s40246-025-00718-9>
16. Shaman JA. The future of pharmacogenomics: integrating epigenetics, nutrigenomics, and beyond. *J Pers Med.* 2024;14(12):1121. <https://doi.org/10.3390/jpm14121121>
17. Lauschke VM, Zhou Y, Ingelman-Sundberg M. Pharmacogenomics beyond single common genetic variants: the way forward. *Annu Rev Pharmacol Toxicol.* 2024;64:33-51. <https://doi.org/10.1146/annurev-pharmtox-051921-091209>
18. Smith DA, Sadler MC, Altman RB. Promises and challenges in pharmacoeugenetics. *Camb Prism Precis Med.* 2023;1:e18. <https://doi.org/10.1017/pcm.2023.6>
19. Trevor GR, Lim YJ, Urquhart BL. Pharmacometabolomics in drug disposition, toxicity, and precision medicine. *Drug Metab Dispos.* 2024;52(11):1187-1195. <https://doi.org/10.1124/dmd.123.001074>
20. Nam Y, Kim J, Jung SH, et al. Harnessing artificial intelligence in multimodal omics data integration: paving the path for the next frontier in precision medicine. *Annu Rev Biomed Data Sci.* 2024;7(1):225-250. <https://doi.org/10.1146/annurev-biodatasci-102523-103801>
21. Ballard JL, Wang Z, Li W, Shen L, Long Q. Deep learning-based approaches for multi-omics data integration and analysis. *BioData Min.* 2024;17(1):38. <https://doi.org/10.1186/s13040-024-00391-z>
22. Aldea M, Friboulet L, Apcher S, et al. Precision medicine in the era of multi-omics: can the data tsunami guide rational treatment decision? *ESMO Open.* 2023;8(5):101642. <https://doi.org/10.1016/j.esmoop.2023.101642>
23. Flores JE, Claborn DM, Weller ZD, Webb-Robertson BM, Waters KM, Bramer LM. Missing data in multi-omics integration: recent advances through artificial intelligence. *Front Artif Intell.* 2023;6:1098308. <https://doi.org/10.3389/frai.2023.1098308>
24. Mohr AE, Ortega-Santos CP, Whisner CM, Klein-Seetharaman J, Jasbi P. Navigating challenges and opportunities in multi-omics integration for personalized healthcare. *Biomedicine.* 2024;12(7):1496. <https://doi.org/10.3390/biomedicine12071496>
25. Anwardeen NR, Naja K, Elrayess MA. Advancements in precision medicine: multi-omics approach for tailored metformin treatment in type 2 diabetes. *Front Pharmacol.* 2024;15:1506767. <https://doi.org/10.3389/fphar.2024.1506767>
26. Heo YJ, Hwa C, Lee GH, Park JM, An JY. Integrative multi-omics approaches in cancer research: from biological networks to clinical subtypes. *Mol Cells.* 2021;44(7):433-443. <https://doi.org/10.14348/molcells.2021.0042>
27. Sopic M, Vilne B, Gerdts E, et al. Multiomics tools for improved atherosclerotic cardiovascular disease management. *Trends Mol Med.* 2023;29(12):983-995. <https://doi.org/10.1016/j.molmed.2023.09.004>
28. Chen C, Wang J, Pan D, et al. Applications of multi-omics analysis in human diseases. *MedComm (2020).* 2023;4(4):e315. <https://doi.org/10.1002/mco.2315>
29. Kan Z, Wen J, Bonato V, et al. Real-world clinical multi-omics analyses reveal bifurcation of ER-independent and ER-dependent drug resistance to CDK4/6 inhibitors. *Nat Commun.* 2025;16(1):932. <https://doi.org/10.1038/s41467-025-55914-x>
30. Yu Y, Zhang N, Mai Y, et al. Correcting batch effects in large-scale multiomics studies using a reference-material-based ratio method. *Genome Biol.* 2023;24(1):201. <https://doi.org/10.1186/s13059-023-03047-z>
31. Liu XY, Mei XY. Prediction of drug sensitivity based on multi-omics data using deep learning and similarity network fusion approaches. *Front Bioeng Biotechnol.* 2023;11:1156372. <https://doi.org/10.3389/fbioe.2023.1156372>
32. Peng W, Chen T, Liu H, Dai W, Yu N, Lan W. Improving drug response prediction based on two-space graph convolution. *Comput Biol Med.* 2023;158:106859. <https://doi.org/10.1016/j.combiomed.2023.106859>
33. Mohammadzadeh-Vardin T, Ghareyazi A, Gharizadeh A, Abbasi K, Rabiee HR. DeepDRA: drug repurposing using multi-omics data integration with autoencoders. *PLoS One.* 2024;19(7):e0307649. <https://doi.org/10.1371/journal.pone.0307649>
34. Joyce JB, Grant CW, Liu D, et al. Multi-omics driven predictions of response to acute phase combination antidepressant therapy: a machine learning approach with cross-trial replication. *Transl Psychiatry.* 2021;11(1):513. <https://doi.org/10.1038/s41398-021-01632-z>
35. Wang C, Zhang M, Zhao J, Li B, Xiao X, Zhang Y. The prediction of drug sensitivity by multi-omics fusion reveals the heterogeneity of drug response in pan-cancer. *Comput Biol Med.* 2023;163:107220. <https://doi.org/10.1016/j.combiomed.2023.107220>
36. Rampásek L, Hidru D, Smirnov P, Haibe-Kains B, Goldenberg A. DrVAE: improving drug response prediction via modeling of drug perturbation effects. *Bioinformatics.*

- 2019;35(19):3743-3751. <https://doi.org/10.1093/bioinformatics/btz158>
37. Ferraro L, Scala G, Cerulo L, Carosati E, Ceccarelli M. MOVIDA: multiomics visible drug activity prediction with a biologically informed neural network model. *Bioinformatics*. 2023;39(7):btad432. <https://doi.org/10.1093/bioinformatics/btad432>
 38. Peng W, Chen T, Dai W. Predicting drug response based on multi-omics fusion and graph convolution. *IEEE J Biomed Health Inform*. 2022;26(3):1384-1393. <https://doi.org/10.1109/JBHI.2021.3102186>
 39. Sharifi-Noghabi H, Zolotareva O, Collins CC, Ester M. MOLI: multi-omics late integration with deep neural networks for drug response prediction. *Bioinformatics*. 2019;35(14):i501-i509. <https://doi.org/10.1093/bioinformatics/btz318>
 40. Wang C, Lye X, Kaalia R, Kumar P, Rajapakse JC. Deep learning and multi-omics approach to predict drug responses in cancer. *BMC Bioinformatics*. 2022;22(suppl 10):632. <https://doi.org/10.1186/s12859-022-04964-9>
 41. Park S, Soh J, Lee H. Super. FELT: supervised feature extraction learning using triplet loss for drug response prediction with multi-omics data. *BMC Bioinformatics*. 2021;22(1):269. <https://doi.org/10.1186/s12859-021-04146-z>
 42. Sammut SJ, Crispin-Otuzar M, Chin SF, et al. Multi-omic machine learning predictor of breast cancer therapy response. *Nature*. 2022;601(7894):623-629. <https://doi.org/10.1038/s41586-021-04278-5>
 43. Wu Y, Chen M, Qin Y. Anticancer drug response prediction integrating multi-omics pathway-based difference features and multiple deep learning techniques. *PLoS Comput Biol*. 2025;21(3):e1012905. <https://doi.org/10.1371/journal.pcbi.1012905>
 44. Koch E, Pardiñas AF, O'Connell KS, et al. How real-world data can facilitate the development of precision medicine treatment in psychiatry. *Biol Psychiatry*. 2024;96(7):543-551. <https://doi.org/10.1016/j.biopsych.2024.01.001>
 45. Shriver SP, Adams D, McKelvey BA, et al. Overcoming barriers to discovery and implementation of equitable pharmacogenomic testing in oncology. *J Clin Oncol*. 2024;42(10):1181-1192. <https://doi.org/10.1200/JCO.23.01748>
 46. Nguyen DG, Morris SA, Hamilton A, et al. Real-world impact of an in-house dihydropyrimidine dehydrogenase (DPYD) genotype test on fluoropyrimidine dosing, toxicities, and hospitalizations at a multisite cancer center. *JCO Precis Oncol*. 2024;8:e2300623. <https://doi.org/10.1200/PO.23.00623>
 47. Leong IUS, Cabrera CP, Cipriani V, et al. Large-scale pharmacogenomics analysis of patients with cancer within the 100,000 genomes project combining whole-genome sequencing and medical records to inform clinical practice. *J Clin Oncol*. 2025;43(6):682-693. <https://doi.org/10.1200/JCO.23.02761>
 48. Nguyen DG, Morris SA, Chen A, et al. Unveiling discrepant and rare dihydropyrimidine dehydrogenase (DPYD) results using an in-house genotyping test: a case series. *J Natl Compr Canc Netw*. 2024;22(4):e247022. <https://doi.org/10.6004/jnccn.2024.7022>
 49. Biswas M, Hossain MS, Ahmed Rupok T, Hossain MS, Sukasem C. The association of CYP2C19 LoF alleles with adverse clinical outcomes in stroke patients taking clopidogrel: an updated meta-analysis. *Clin Transl Sci*. 2024;17(4):e13792. <https://doi.org/10.1111/cts.13792>
 50. Claassens DMF, Vos GJA, Bergmeijer TO, et al. A genotype-guided strategy for oral P2Y12 inhibitors in primary PCI. *N Engl J Med*. 2019;381(17):1621-1631. <https://doi.org/10.1056/NEJMoa1907096>
 51. Zhang J, Wu T, Chen W, Fu J, Xia X, Chen L. Effect of gene-based warfarin dosing on anticoagulation control and clinical events in a real-world setting. *Front Pharmacol*. 2019;10:1527. <https://doi.org/10.3389/fphar.2019.01527>
 52. Wang X, Tang B, Zhou M, et al. Efficacy and safety of genotype-guided warfarin dosing versus non-genotype-guided warfarin dosing strategies: A systematic review and meta-analysis of 27 randomized controlled trials. *Thromb Res*. 2022;210:42-52. <https://doi.org/10.1016/j.thromres.2021.12.023>
 53. Swen JJ, van der Wouden CH, Manson LE, et al. A 12-gene pharmacogenetic panel to prevent adverse drug reactions: an open-label, multicentre, controlled, cluster-randomised crossover implementation study. *Lancet*. 2023;401(10374):347-356. [https://doi.org/10.1016/S0140-6736\(22\)01841-4](https://doi.org/10.1016/S0140-6736(22)01841-4)
 54. Murugan M, Yuan B, Venner E, et al. Empowering personalized pharmacogenomics with generative AI solutions. *J Am Med Inform Assoc*. 2024;31(6):1356-1366. <https://doi.org/10.1093/jamia/ocae039>
 55. Keat K, Venkatesh R, Huang Y, et al. PGxQA: a resource for evaluating LLM performance for pharmacogenomic QA tasks. *Pac Symp Biocomput*. 2025;30:229-246. https://doi.org/10.1142/9789819807024_0017
 56. Verkerk K, Voest EE. Generating and using real-world data: a worthwhile uphill battle. *Cell*. 2024;187(7):1636-1650. <https://doi.org/10.1016/j.cell.2024.02.012>
 57. Molla G, Bitew M. Revolutionizing personalized medicine: synergy with multi-omics data generation, main hurdles, and future perspectives. *Biomedicine*. 2024;12(12):2750. <https://doi.org/10.3390/biomedicine12122750>
 58. Dhieb D, Bastaki K. Pharmacogenomics: a new frontier in precision psychiatry. *Int J Mol Sci*. 2025;26(3):1082. <https://doi.org/10.3390/ijms26031082>
 59. Wan Z, Hazel JW, Clayton EW, Vorobeychik Y, Kantarcioglu M, Malin BA. Sociotechnical safeguards for genomic data privacy. *Nat Rev Genet*. 2022;23(7):429-445. <https://doi.org/10.1038/s41576-022-00455-y>
 60. Allen B. The promise of explainable AI in digital health for precision medicine: a systematic review. *J Pers Med*. 2024;14(3):277. <https://doi.org/10.3390/jpm14030277>
 61. Mennella C, Maniscalco U, De Pietro G, Esposito M. Ethical and regulatory challenges of AI technologies in healthcare: a narrative review. *Heliyon*. 2024;10(4):e26297. <https://doi.org/10.1016/j.heliyon.2024.e26297>
 62. Ramirez AH, Suleiman L, Schlueter DJ, et al. The all of us research program: data quality, utility, and diversity. *Patterns*. 2022;3(8):100570. <https://doi.org/10.1016/j.patter.2022.100570>
 63. Asimwe IG, Pirmohamed M. Ethnic diversity and warfarin pharmacogenomics. *Front Pharmacol*. 2022;13:866058. <https://doi.org/10.3389/fphar.2022.866058>
 64. Magavern EF, Gurdasani D, Ng FL, Lee SSJ. Health equality, race and pharmacogenomics. *Br J Clin Pharmacol*. 2022;88(1):27-33. <https://doi.org/10.1111/bcp.14983>
 65. Gao Y, Sharma T, Cui Y. Addressing the challenge of biomedical data inequality: an artificial intelligence perspective. *Annu Rev Biomed Data Sci*. 2023;6:153-171. <https://doi.org/10.1146/annurev-biomedsci-020722-020704>
 66. Smith LA, Cahill JA, Lee JH, Grait K. Equitable machine learning counteracts ancestral bias in precision medicine. *Nat Commun*. 2025;16(1):2144. <https://doi.org/10.1038/s41467-025-57216-8>
 67. Asimwe IG, Zhang EJ, Osanlou R, et al. Genetic factors influencing warfarin dose in black-African patients: a systematic review and meta-analysis. *Clin Pharmacol Ther*. 2020;107(6):1420-1433. <https://doi.org/10.1002/cpt.1755>
 68. Liao J, Li X, Gan Y, et al. Artificial intelligence assists precision medicine in cancer treatment. *Front Oncol*. 2022;12:998222. <https://doi.org/10.3389/fonc.2022.998222>
 69. Gschwind A, Ossowski S. AI Model for Predicting Anti-PD1 Response in Melanoma Using Multi-Omics Biomarkers. *Cancers (Basel)*. 2025;17(5):714. <https://doi.org/10.3390/cancers17050714>
 70. Osipov A, Nikolic O, Gertych A, et al. The molecular twin artificial-intelligence platform integrates multi-omic data to predict outcomes for pancreatic adenocarcinoma patients. *Nat Cancer*. 2024;5(2):299-314. <https://doi.org/10.1038/s43018-023-00697-7>

71. Singh S, Stocco G, Theken KN, et al. Pharmacogenomics polygenic risk score: ready or not for prime time? *Clin Transl Sci*. 2024;17(8):e13893. <https://doi.org/10.1111/cts.13893>
72. Babu M, Snyder M. Multi-omics profiling for health. *Mol Cell Proteomics*. 2023;22(6):100561. <https://doi.org/10.1016/j.mcpro.2023.100561>
73. Wang E, Schmidgall S, Jaeger PF, et al. TxGemma: efficient and agentic LLMs for therapeutics. *Preprint*. Posted online April 8, 2025. <https://doi.org/10.48550/arXiv.2504.06196>
74. Ooka T. The era of preemptive medicine: developing medical digital twins through omics, IoT, and AI integration. *JMA J*. 2025; 8(1):1-10. <https://doi.org/10.31662/jmaj.2024-0213>