JOURNAL OF APPLIED BIOANALYSIS, October 2025, p. 1165-1176
http://doi.org/10.53555/jab.v11si2.702 (ISSN 2405-710X)
Vol. 11, No. S2

OPEN ACCESS

AI-Integrated Molecular Pharmacovigilance in Immuno-Oncology: A Biochemical and Genomic Perspective

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ABSTRACT

Background: Immunotherapy has revolutionized the management of cancer, whereas immune-related adverse events(irAEs) are a significant issue when it comes to patient safety. Traditional pharmacovigilance is very reactive and incapable of predicting these complex and delayed toxicities. The advent of artificial intelligence (AI) has portended Onco-Immuno-Pharmacovigilance, which combines oncology, immunology and pharmacovigilance to predict safety in the form of future monitoring. At the molecular level, immune-checkpoint inhibitors (anti-PD-1, anti-CTLA-4) interfere with immune tolerance through changing cytokine signaling (IL-6, IFN- 7, TNF- 6) and T-cell metabolism. These are regulated by genetic variation in HLA locus and CTLA4 and biochemical indicators of early immune toxicity in ALT, LDH and IDO1.

Objective: To summarize the development of AI-based molecular pharmacovigilance, it is important to highlight the need to combine biochemical pathways, genetic determinants and multi-omics data into AI models to predict immunotherapy-related toxicities in a mechanistic manner.

Methods: The databases such as PubMed, Scopus, WHO-VigiBase, and FDA-FAERS were searched (2018-2025) on AI and immunotherapy and adverse drug reactions studies. The preference was to include research based on the use of molecular biomarkers, groups of cytokines, enzyme tests or the use of genomic variations associated with immune toxicity.

Results: Machine-learning models including genetic variations, cytokine, and enzyme assays were more accurate in early warning of irAE and predicting hepatotoxicity or pneumonitis. Mechanism validation of predictions made by AI derived prediction was mechanistically

validated through molecular analysis of HLA alleles, IL-6 and LDH/IDO1 activity. There are still significant weaknesses such as bias, lack of interpretability and missing data. Conclusion: Molecular pharmacovigilance is an AI that enhances pharmacovigilance beyond a statistical surveillance approach to biochemical, genetic, and mechanistic accuracy and permits the biologically meaningful and patient-specific safety surveillance by interdisciplinary cooperation.

Keywords: Artificial Intelligence, Immunotherapy, Pharmacovigilance, Onco-Immuno-Pharmacovigilance, Precision Oncology

INTRODUCTION

Although most of the respondents viewed migration as something unavoidable in the lives of the hills, a way to shift migration would be achieved in case there were decent local opportunities formed. The young people would always say that they would prefer to remain in their villages as long as there were good and respectable livelihoods there. A number of the returnees were interested in small-scale enterprises such as eco-tourism, organic farms and online education but pointed out that such enterprises require institutional and financial support to make them viable. Migration is not inborn according to this argument, yet immensely rooted. Migration drive is a phenomenon that can even be reduced through certain investments, quality education and context-sensitive policy interventions. It is not preventing migration but making it voluntary and not forced by circumstances, and it is fitting migration into the voluntary dimension and not the necessity dimension so that people could stay voluntarily and not by coercion. Regional inequality tendencies and new migration patterns provide evidence that mobility in Uttarakhand is a side effect and a result of unequal development. The next section contains the conclusion of these results and defines the most significant emerging views and unites the historical, demographic, economic and policy factors to give the full picture on migration as structural change within the state. In contrast to traditional chemotherapy toxicities, irAEs are unpredictable, immune-mediated, and can occur weeks or months after the start of therapy, making causality evaluation challenging (Chen et al., 2023).

At the molecular biology level, immune-related adverse events (irAEs) result from immune tolerance pathways dysregulation at the cellular and gene level. Autoreactive $CD4^+$ and $CD8^+$ T-cells are activated due to loss of peripheral tolerance, and reactive oxygen species levels are raised, leading to apoptotic and necrotic cascades in normal tissues. Epigenetic modulation, such as changed microRNA expression and DNA methylation patterns, even more highly activates inflammatory gene transcription. Insight into these biochemical and genetic dysfunctions forms the mechanistic underpinning for predictive safety model development using AI.

Classic pharmacovigilance systems like WHO-VigiBase, FDA's FAERS, and PvPI of India mainly use spontaneous adverse event reporting and signal detection algorithms (Wang et al., 2024). Although these databases are still vital, they are subject to major limitations in the biologics and age of personalized medicine, such as underreporting, unstructured data, and failure to integrate with genomics and imaging biomarkers (Sato et al., 2023). Traditional pharmacovigilance hardly includes biochemical markers or molecular-level information like cytokine panels, enzyme levels (ALT, AST, LDH), or genomic variants with toxicities. The molecular biomarker analysis combined with the AI technology can help bridge an important gap, as we can detect patterns not only on the basis of clinical data but also on the basis of the protein interactions, gene expression patterns and metabolite analysis. The last decade has seen the combination of Artificial Intelligence (AI) and machine learning (ML) in pharmacovigilance allowing automatic identification of concealed patterns in large sets of real-world information (Topol, 2019). The algorithms of AI can be used to search unstructured clinical texts, electronic health records (EHRs), and post-marketing surveillance data to forecast the risk of adverse events, discover drug-event interactions, and detect initial safety signals (U.S. Food and Drug Administration, 2024). This thrilling union of oncology, pharmacology, immunology and computational science has borne a new name known as Onco-Immuno-Pharmacovigilance. It is an area of intersection between the conventional pharmacovigilance and the AI analytics to predict, prevent and personalize drug safety in cancer treatment (European Medicines Agency, 2025). Such an interdisciplinary method can change the current situation of pharmacovigilance, turning it into a much more proactive approach that would not only effectively save lives but also be safe. Therefore, the combination of biochemistry, genetics, and molecular biology in AI-based pharmacovigilance can be viewed as a new era of the mechanism-based science of safety. Onco-Immuno-Pharmacovigilance goes beyond statistical analysis to adopt the actual molecular-systems pharmacology by unraveling immune signaling networks, gene-drug interactions, and biochemical signs of toxicity.

MECHANISMS OF IMMUNOTHERAPY-INDUCED TOXICITY:

The fundamental concept of cancer immunotherapy is to stimulate those slumbering or suppressed immune reactions to become active so that they can identify and destroy tumour-related antigens. The thing is that here is the trap: the same immune activation that is useful to destroy tumors, may attack healthy tissues mistakenly, causing immune-related adverse events (irAEs). They may have diverse reactions, including mild skin rashes to such severe diseases as pneumonitis, myocarditis, or colitis (Weber et al., 2015).

Immune Checkpoint Dysregulation

The immune checkpoint blockers (ICBs) are anti-CTLA-4 and anti-PD-1/PD-L1 antibodies, which operate through the elimination of the suppressive signals that typically prevent autoimmunity. This peripheral tolerance loss may trigger the autoreactive T-cells and release of the inflammatory cytokines such as IFN- 7, TNF- 7 and IL-17 (Michot et al., 2016). When activated, these cytotoxic lymphocytes have the ability to attack different organs, causing inflammation in them and tissue damage. At the biochemical level, the inhibition of these immune checkpoints modulates metabolic and signaling pathways in the activated T-cells. Due to high glycolysis, glutaminolysis, and fatty acid oxidation, an excessive immune response is observed, and decreased oxidative phosphorylation leads to the formation of reactive oxygen species (ROS) and mitochondrial stress. Such alterations may cause lipid peroxidation and DNA damage of normal tissues, triggering inflammatory cascades. Also, the alteration of the JAK–STAT, PI3K-AKT, and NF-KB signaling leads to the release of pro-inflammatory cytokines and death of parenchymal cells, which is the biochemical basis of immune-mediated toxicity.

Cytokine Storm and Hyperactivation

Certain treatment methods, particularly CAR-T cell therapies and bispecific antibodies, result in a massive cytokine release, causing cytokine-release syndrome (CRS) and immune effector cell-associated neurotoxicity (ICANS) (Neelapu et al., 2018). CRS is attributed to excessive production of IL-6, IL-1, and GM-CSF that lead to such symptoms as fever, low blood pressure, and multiple organ failures. The pathogenesis of a cytokine storm, biochemically, entails excessive immune response. The hyper-physiologic cytokine load disturbs vascular endothelial cell tight junctions, enhances nitric oxide synthase (NOS) activity and leads to capillary leakage. This systemic biochemical homeostasis malady is the cause of the metabolic derangements of severe CRS and ICANS. The most important point is the timely identification and treatment to prevent deaths (Shimabukuro-Vornhagen et al., 2018).

Molecular Mimicry and Cross-Reactivity

In some cases, tumour cells and normal cells may have similar antigenic epitopes and hence cross-reactivity of activated T-cells and antibodies. One interesting instance of this is the cardiac and skeletal muscle toxicity observed in melanoma patients receiving the checkpoint inhibitor. This is because it shares some antigens with melanocytes and myocytes (Salem et al., 2019). The present type of cross-reactive autoimmunity emphasizes the homology of peptide sequence between tumor proteins and those of the host. The antigenic motifs and molecular mimicry have been demonstrated to overlap at the MHC-binding level through immunopeptidomic studies.

Genetic and Epigenetic Susceptibility

In the case of genetic and epigenetic predisposition, the genetics of the host are major and determine the risk of adverse events of immune-related adverse events (irAEs). Some HLA types, including HLA-DRB111:01 and HLA-B35:01, and also CTLA4 polymorphism, have been associated with an increased risk of autoimmune hepatitis and endocrinopathies (Baxi et al., 2018). Also, immune tolerance can be affected through the epigenetic processes, the dysregulation in the expression of microRNA, as well. In addition to HLA and CTLA4 polymorphisms, other new epigenetic indicators, including deregulation of histone acetylation (H3K27ac) and microRNA expression changes (such as miR-155 and miR-146a), have been implicated in toxicity caused by checkpoint inhibitors. These mutations have the capacity to control the expression of pro-inflammatory cytokines (IL1B, IL6, TNFA) and immune checkpoint genes, which influence therapeutic outcomes and immunity to irAEs. With these genetic and epigenetic signatures incorporated into the pharmacovigilance models, we can develop a molecular platform of risk prediction.

Predictive Modelling Integration

Regarding the integration on the predictive modelling front, AI methods can make use of this mechanistic knowledge to come up with predictive models on toxicity. Machine-learning models can be used to distinguish between high-risk and low-risk patients before administering any therapy through the addition of cytokine signatures, HLA data, and treatment parameters (Liang et al., 2023). Such mechanistic understandings can be used to include biochemical and molecular features, including cytokine dynamics, gene expression dynamics, and metabolomic dynamics, in AI models.

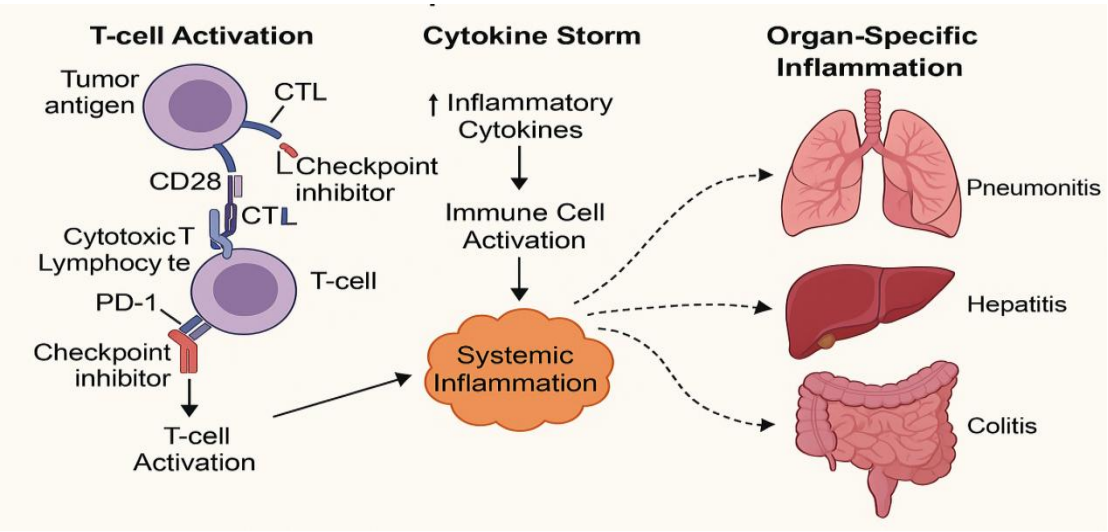

Figure 1: Toxicities induced by checkpoint inhibitors: The mechanisms include T-cell stimulation, cytokine storm, and inflammation targeted to the organ.

ROLE OF ARTIFICIAL INTELLIGENCE IN PREDICTIVE PHARMACOVIGILANCE:

Artificial Intelligence (AI) has become a crucial part of the analytic tool in modern pharmacovigilance, transforming how data on safety is gathered, processed, and interpreted. It can process large, heterogeneously composed collections of data, clinical stories, electronic health records (EHRs), spontaneous reporting systems (SRS) and even social media to identify patterns that a person reviewer can easily overlook (Zhang et al., 2022). Importantly, computational methods are currently being used to calculate biochemical and molecular data, including cytokine panels, proteomic biomarkers, and genomic polymorphisms, to give more insight into the molecular aspects of drug toxicity.

Machine Learning for Signal Detection

Machine learning (ML) models such as random forests, support vector machines (SVMs), gradient boosting algorithms, have been found with increased capacity in identifying adverse drug reaction (ADR) signs in large pharmacovigilance databases. Trained on FAERS, EudraVigilance, and VigiBase, ML-based models can be used to predict the likelihood of drug-event relations in oncology, basing predictions on the co-reported toxicities, dosage patterns, and temporal patterns (Liu et al., 2023). In molecular terms, the ML algorithms have been in a position to match the pattern of gene-expression and levels of serum biomarkers with specific negative events. As an illustration, the HLA variants, IL-6 levels, and liver enzyme (ALT, AST) activities combined with random forests were more useful in predicting immune-mediated hepatitis. These results illustrate how machine learning has the potential to combine clinical, biochemical, and genetic factors into one predictive model.

One research applied an ML classifier to identify immune checkpoint inhibitor-associated pneumonitis with a predictive accuracy of more than 80% by integrating structured and unstructured EHR data. These platforms offer automated prioritization of "high-signal" drug-event pairs for regulatory assessment, hence expediting risk management (Liu R et al., 2023).

Natural Language Processing (NLP) and Text Mining

Much of ADR information is in free-text format (e.g., discharge summaries, case notes, narrative reports). NLP techniques identify key entities like drug names, symptoms, and temporal relationships. For example, NLP-enabled pharmacovigilance systems on oncology data have been able to reveal unsuspected immune-mediated effects, including endocrinopathies and dermatologic effects (Morita et al., 2022). Such automated text mining enhances the completeness of pharmacovigilance, minimizing reliance on voluntary human reporting. Current advances in molecular natural language processing (molNLP) push text mining to pull biochemical terms, genetic variants, and pathway data from literature into automated drug–gene–biomarker mapping and hypothesis generation for molecular pharmacovigilance.

Deep Learning and Neural Networks

Deep learning (DL) architectures, particularly convolutional neural networks (CNNs) and recurrent neural networks (RNNs), facilitate sophisticated feature extraction from clinical imaging, pathology slides, and genomics (Razzak et al., 2020). These models can connect radiomic and genomic biomarkers to toxicity signatures so that clinicians can see the relationship between immune activation and radiologic inflammation (Tan Y et al., 2023). In addition, multi-omics deep-learning frameworks integrate transcriptomic, proteomic, and metabolomic information to recognize mechanistic

signatures of toxicity. For instance, autoencoder-based neural networks have associated metabolic enzyme dysregulation (LDH, IDO1) with checkpoint inhibitor hepatotoxicity and colitis. This type of integration shows that deep learning can uncover weak signals of clinical adverse events, the likes of which are indicated by a correlation between biochemical factors. Clinical decision support systems (CDSS) are also integrating AI-based prediction platforms and are used to give real-time notifications during immunotherapy treatment. Detecting the at-risk patients will allow the doctors to modify the dose or monitor specific biomarkers in advance, which is the shift to predictive pharmacovigilance (Banerjee et al., 2024).

Data Fusion and Real-World Integration

The use of AI outputs in pharmacovigilance reports, real-world evidence (RWE), and multi-omics datasets has resulted in a novel model of data fusion. It increases the validity of signals through linking clinical observations and biological plausibility. Further privacy and scalability are provided by the incorporation of federated learning models where AI algorithms are trained across a number of hospitals without the transfer of patient data to a central location (Singh N et al., 2023). Overall, these methods demonstrate how AI would enhance pharmacovigilance to predictive real-time ecosystem rather than descriptive reporting, fully complying with the mission of Onco-Immuno-Pharmacovigilance. Overall, AI-driven predictive pharmacovigilance is no longer statistics surveillance because it incorporates biochemical, genomic, and molecular biology data streams. The synergy between multi-omics analytics and machine intelligence turns pharmacovigilance into a systems-level molecular safety science that can uncover causal drug-gene-cellular metabolism relationships.

Table 1: AI techniques and their pharmacovigilance applications in oncology.

AI Method	Data Source	Key Application	Example Output
Machine Learning (Random Forest, SVM)	FAERS, VigiBase	Signal detection	ADR risk probability models
NLP	Clinical notes, case reports	Extracting hidden ADRs	Text-mined irAE detection
Deep Learning (CNN, RNN)	Imaging, omics data	Toxicity pattern recognition	Predictive imaging biomarkers
Bayesian Networks	Real-world registries	Causality estimation	Probabilistic drug-event mapping

INTEGRATION OF PHARMACOGENOMICS AND AI FOR PREDICTIVE MODELING:

The discipline of pharmacogenomics seeks to know the ways through which genetic differences affect drug response, toxicity, and metabolism (Daly AK & Day CP, 2019). Genomic heterogeneity plays an important role in determining the sensitivity or susceptibility to any form of treatment in cancer besides being a determinant of treatment effectiveness. Pharmacogenomics can be used to conduct a risk assessment that is more precise and adapted to a patient, which is possible only with the integration of AI analytics (Zhernakova et al., 2022). Biochemically and molecularly, pharmacogenomic differences affect not just gene expression but also downstream protein structure, receptor binding affinity, and metabolic enzyme kinetics. Gene polymorphisms for cytochrome P450 enzymes (CYP3A4, CYP2D6) and drug transporters (ABCB1, SLCO1B1) modify immunotherapy pharmacokinetics to cause differences between individuals in drug metabolism, plasma half-life, and thresholds of immune activation. These biochemical differences at the enzyme and receptor level are the basis for much of the observed genetic variation in susceptibility to adverse events.

Genetic Determinants of Immunotherapy Toxicity

The molecular immunogenetics of immune checkpoints offers a basis for relating genotypic variation to biochemical immune reactions. Specific human leukocyte antigen (HLA) alleles and polymorphisms of immune-regulatory genes predispose patients to **immune-related adverse events (irAEs)** (Hosoya N et al., 2022). On an example, autoimmune hepatitis induced by nivolumab has been linked to HLA-DRB11:01, whereas endocrine toxicities are linked to CTLA4 rs231775 (Yoshin K et al., 2023). PDCD1 and IL6R variants of genes have also been linked to pneumonitis and cytokine-release syndrome respectively (Lin J et al., 2023). These results indicate

that irAEs is not a chance, but a determined by genetics phenomenon, the outcome of immunogenetic profile of the patient. When incorporated in the AI algorithms, such markers would make the prediction more precise and permit stratified monitoring. Along with HLA and checkpoint-related genes, functional variants of cytokine-signaling receptors (including IL6R, STAT3 and JAK1) regulate biochemical signaling cascades which regulate the intensity of cytokine release and metabolism of immune-cells. Such molecular interactions can be learnt by AI algorithms and can recognize how variation on a gene level is translated into biochemical toxicity phenotypes.

AI-Enhanced Pharmacogenomic Modeling

Genomic models made by AI can identify nonlinear and complex associations between multiple genetic variants and the results of toxicity (Chen Q et al., 2023). At biochemical level, these AI models transfer changes at the pathway level by mapping out transcriptomic and proteomic data to genetic variants. For example, increased expression of IDO1, LDH, and IFN-γ–regulated enzymes has been mechanistically associated with T-cell exhaustion and metabolic stress on immune overactivation. The inclusion of such molecular biomarkers enables AI models to make more accurate predictions for immune-mediated organ injury.

- Random Forest and Support Vector Machine models predicted immune-mediated hepatitis with up to 85% accuracy when HLA alleles were considered as input features.
- Neural networks are capable of handling large-scale genomic data to detect combinatorial variant effects that would go undetected.

Through combining clinical, genomic, and laboratory characteristics, multi-modal AI platforms attain higher sensitivity in predicting severe irAEs than conventional regression models (Wang CY et al., 2024). This merger of multi-omics data sets (genomics, proteomics, metabolomics) reconstitutes pharmacovigilance as descriptive monitoring into a molecular-systems science, which can discover biochemical feed-back loops prior to clinical toxicity.

Table 2: Selected pharmacogenomic biomarkers and AI-aided Accuracy for immunotherapy-toxicities.

Marker	Toxicity	Algorithm	Accuracy	Reference
HLA-DRB1*11:01	Hepatitis (Nivolumab)	Random Forest	85	Sato et al., 2023
CTLA4 rs231775	Endocrinopathy	SVM	78	Liang et al., 2023
PDCD1 PD-1.6	Pneumonitis	Logistic Regression + NLP	81	Wang et al., 2024

Toward Genomic-AI Integration in Clinical Workflows

The intersection of pharmacogenomics and AI signals the shift from population-level to personalized pharmacovigilance. Through pre-treatment identification of high-risk genotypes, clinicians can personalize dosing, choose alternative drugs, or apply pre-emptive monitoring (Ghosh R et al., 2023). From the interface of molecular biology, genomic-AI models decode how immune-checkpoint gene expression and enzyme activity interplay to modulate treatment outcomes. This provides biochemical insight into the mechanisms of drug response to allow predictive modeling to not divorce itself as molecular physiology but instead be founded on it as compared to statistical inference. Despite this, it cannot be integrated easily into standard oncology practice due to the lack of access to genomic sequencing, lack of standardized bioinformatics architecture, and the need to have XAI structures (Lee H et al., 2024). Despite this, precision drug safety is the future of AI-pharmacogenomic synergy.

CLINICAL IMPLEMENTATION CHALLENGES:

Although Onco-Immuno-Pharmacovigilance can be a groundbreaking concept in cancer safety monitoring based on AI, in reality, the implementation is not easy due to the number of technical, clinical, and ethical limitations (Liao J et al., 2023). Bringing molecular and biochemical discoveries to operational clinical workflows is still a core challenge. Though predictive models detect genetic polymorphisms and biochemical markers (e.g., cytokines, enzymes, and metabolites) linked with immune toxicities, they are not being implemented in hospital labs. To standardize biomarker quantification procedures, such as cytokines (IL-6, TNF-alpha), enzyme activity screens (ALT, LDH, IDO1), and oxidative stress biomarkers are needed to be standardized across clinical environments. In the absence of this biochemical

validation, AI-based models will tend to lose biological accuracy even with a robust computational performance.

Data Heterogeneity and Quality Issues

Pharmacovigilance data are very heterogeneous and come from electronic health records (EHRs), case reports, registries, and laboratory databases. Data format variability, missing information, and non-uniform terminology hinder algorithmic learning and diminish model accuracy. In addition, spontaneous reporting systems (SRS) suffer from under-reporting, particularly for delayed-onset immune-related toxicities (Bousquet C et al., 2024). Standardizing clinical terminologies with MedDRA and SNOMED-CT ontologies is needed for interoperability among datasets (Challen R et al., 2019). Aside from inconsistencies of data formats, molecular and biochemical heterogeneity is the other obstacle to trusted integration. Batch effects are produced by variations in sample preparation, reagent calibration, RNA extraction efficiency, and mass-spectrometry proteomic sensitivity, which alter molecular readouts. AI platforms must thus include biochemical normalization algorithms to reduce variation between laboratories so that molecular profiles (e.g., cytokine levels, transcript levels) are directly comparable across studies.

Algorithmic Bias and Generalizability

The majority of AI algorithms are developed based on datasets obtained from restricted geographical locations or limited ethnic groups. This creates algorithmic bias, as the predictions won't generalize across various groups of patients (Mehrabi N et al., 2021). It is possible that an AI algorithm trained on primarily Western cohorts will perform poorly when it is used in Indian or Asian cohorts with different pharmacogenomic profiles. Reducing bias necessitates multi-ethnic, multi-reality training data sets and federated learning models that enable international data collaboration without compromising confidentiality (Linardatos et al., 2023). Algorithmic bias is also magnified by molecular-level heterogeneity. Different genetic backgrounds, isoforms of enzymes, and cytokine kinetics among ethnic groups can affect biochemical reactions to immunotherapy. As such, AI models that have learned mostly from Western molecular datasets could miss variant-dependent biochemical pathways that are important in Asian or Indian populations. Providing population-specific molecular reference ranges for major biomarkers (IL-6, HLA-DRB1 alleles, and metabolic enzymes) would enhance generalizability and biological fairness.

Explainability and Trust in AI Decisions

One of the most enduring difficulties is the "black-box" nature of deep-learning algorithms. Clinicians may be hesitant to make decisions based on uncertain reasoning paths. Explainable AI (XAI) tries to address this shortcoming by making it explicit how features used were most responsible for toxicity prediction, thus boosting clinician confidence (European Parliament, 2025). In addition to algorithmic transparency, explainability in molecular pharmacovigilance also demands that AI results refer to biochemical or genetic proof. As an example, a model used to predict hepatotoxicity ought to emphasize the mechanistic molecular features, e.g., elevated ALT/AST activity, enhanced IL-6 signaling, or a CTLA4 variant that guided the prediction. Such interpretability at the mechanistic level brings recommendations in line with molecular biology and enhances clinician confidence in data-driven solutions. Interpretable dashboards implemented within hospital information systems can improve clinical trust and usability.

Ethical and Privacy Concerns

Inclusion of big patient data in AI systems triggers ethical issues of consent, sharing of data, and privacy (World Health Organization, 2023). De-identification measures usually fall short in genomic data where re-identification threat remains (Indian Pharmacopeia Commission, 2024). There is a need for compliance with GDPR (Europe) and the Indian Data Protection Acts to ensure ethical deployment of AI. Federated learning and blockchain audit trails also present new solutions for secure and transparent management of data (Ministry of AYUSH, 2024). Molecular systems for pharmacovigilance also need special protection for genomic and biochemical information, which can expose heritable characteristics or predispositions to disease. Ethical guidelines must thus incorporate molecular data encryption, access-controlled repositories, and direct patient consent for utilization of genomic or proteomic data in AI training sets.

Implementation Barriers in Low- and Middle-Income Countries (LMICs)

In LMICs, such as India, fewer resources, limited data scientist talent, and minimal high-performance computing capabilities hinder AI uptake. The pharmacovigilance centers such as PvPI and PPvAYUSH have a slow introduction of AI analytics, but the scalability problem remains (Bittner et al., 2023). These gaps in knowledge and technology can be bridged by public-private relationships and international alliances. Biochemical infrastructure and molecular diagnostic capacity building is also one of the ways through which implementation bottlenecks are overcome. The existence of inexpensive laboratory services to conduct molecular assays i.e. cytokine profiling and pharmacogenetic test would allow local validation of AI models with regard to safety. The establishment of more robust

partnerships between biochemistry and AI in LMICs will support the global representation of molecular data, which will provide fair access to accuracy in pharmacovigilance.

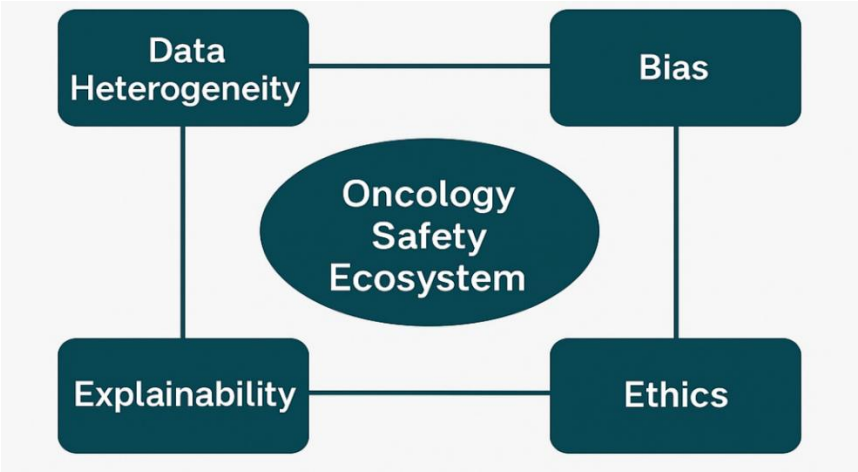

Figure 2: Data heterogeneity, bias, explainability, and ethical issues are challenges in AI-based pharmacovigilance, which are closely linked in the oncology safety ecosystem.

REGULATORY AND ETHICAL FRAMEWORK:

Effective AI-powered Onco-Immuno-Pharmacovigilance can only become a reality due to robust regulatory practices, ethical principles, and global harmonization of the data. The health officials across the globe have realized the need to adopt structures that are adaptive in nature to ensure that emerging technologies are used to enhance patient safety rather than erode it.

United States- FDA Sentinel and Real-World Evidence (RWE) Initiatives

In 2008, the U.S. Food and Drug Administration (FDA) launched the Sentinel Initiative in order to proactively oversee post-marketing safety by using real-world data (RWD). The initiative has since been expanded to utilize AI and machine-learning models for real-time signal detection and adverse event forecasting in oncology therapeutics. The FDA's 2024 update focused on the application of AI-based causal inference models and Bayesian analysis to detect patterns in irAE clusters of checkpoint inhibitors and CAR-T treatments. In addition, the agency's Digital Health Innovation Action Plan promotes open algorithm validation and clinician interpretability for all AI systems deployed in pharmacovigilance.

European Union- EMA's DARWIN EU and AI Governance

The European Medicines Agency (EMA) launched DARWIN EU (Data Analysis and Real-World Interrogation Network) to consolidate AI-based safety analytics in European healthcare systems. The network uses federated learning to process decentralized oncology data without exchanging patient-level information. The EU AI Act (2025) classifies pharmacovigilance systems as "high-risk AI", subjecting them to strict performance monitoring, transparent algorithm design, and traceable data provenance. As pharmacovigilance extends to cover molecular and biochemical information like genomic sequences, proteomic fingerprints, and cytokine profiles, regulatory paradigms will have to adapt to establish standards for protection of biological data and validation of laboratory data. Achieving international agreement on accrediting molecular assays and omics-data reproducibility will guarantee that AI-based systems continue to be ethically sound yet scientifically stringent.

World Health Organization- Global Harmonization of Smart PV

The World Health Organization (WHO), via its Uppsala Monitoring Center (UMC), has integrated AI-driven signal prioritization into VigiBase, the largest ADR database globally. The WHO "Smart Pharmacovigilance Initiative" focuses on harmonizing AI algorithms at the global level in order to enable early detection of signals for biologics and immunotherapies in heterogeneous populations.

India - PvPI, PPvAYUSH, and National Digital Health Mission

India's Pharmacovigilance Program of India (PvPI) under the Indian Pharmacopeia Commission (IPC) is also applying AI tools for real-time monitoring of adverse events. The PPvAYUSH program applies these analytics to non-traditional systems such as Ayurveda and Siddha, in support of integrative drug safety surveillance. The National Digital Health Mission (NDHM) also facilitates centralized access

to anonymized EHR data, in support of AI-based pharmacovigilance research.

Ethical and Legal Safeguards

Ethical leadership is needed to ensure transparency, accountability, and patient self-determination. AI systems need to be guided by principles of beneficence (improving patient safety), non-maleficence (minimizing harm), and justice (minimizing bias in predictions). Regulatory bodies increasingly are requesting algorithm explainability reports, bias audits, and post-market surveillance of AI to deliver fairness. As AI moves from research to regulation, harmonization of global agencies FDA, EMA, WHO, and country-specific pharmacovigilance centers will seal the fate of Onco-Immuno-Pharmacovigilance as a safe, ethical, and transparent science.

FUTURE DIRECTIONS:

Onco-Immuno-Pharmacovigilance is rapidly developing due to the technological level, the democratization of data, and integrative AI systems. The vision of the future intends to move away towards the retrospective ADR documentation and move to real-time, proactive safety prediction, using real-time patient monitoring and advanced analytical models.

Explainable Artificial Intelligence (XAI)

Common deep-learning models are typically black boxes, that is, they make predictions but cannot be interpreted in any way 85. Explainable AI (XAI) provides transparency by identifying variables and clinical parameters that make a prediction. SHAP (Shapley Additive Explanations) and LIME (Local Interpretable Model-Agnostic Explanations) are currently being used to interpret AI results in pharmacovigilance oncology. The presence of XAI makes AI recommendations clinically understandable, increasing physician trust and acceptance by regulators.

Integration of Wearable Sensors and Mobile Health (mHealth)

The future pharmacovigilance is not only inside the hospitals. Physiological parameters measured by wearable biosensors and mobile health (mHealth) systems such as heart rate variability, temperature, and skin changes can be monitored continuously, and the onset of toxicity can be detected. These streams of data can be processed in real-time by AI algorithms and give alerts about the negative trends even before the clinical deterioration occurs. Crowdsourced ADR reporting will also be possible through patient-centric mobile applications, which will improve the richness and timeliness of data.

Multi-Omics Integration for Predictive Modeling

Multi-omics data, including genomics, transcriptomics, proteomics and metabolomics will be incorporated into future AI models to make predictions of immune-related toxicities on a molecular level. As an example, the early immune dysregulation patterns, related to specific drug mechanisms, can be detected with the help of AI-enhanced single-cell RNA sequencing (scRNA-seq). With a combination of omics and clinical data, precision pharmacovigilance will become a systems-level science capable of even anticipating toxicities before drug approval.

International Collaboration and Federated Learning

Future pharmacovigilance will be based on international collaboration between regulatory bodies, hospitals and academia. The federated learning platforms allow AI models to be trained on data sources spread geographically without losing data privacy. This form of cross-border integration makes heterogeneous, representative learning possible to reduce bias in algorithms and maximize their generalizability. The projects that can demonstrate the step in the direction of the global community are Darwin EU and WHO Smart PV which focuses on creating interoperative, AI-based pharmacovigilance networks.

Human-AI Synergy in Clinical Decision Making

In spite of the AI abilities, the human knowledge remains in the heart of the clinical safety evaluation. The most appropriate model is collaborative intelligence (cAI), where AI is used to provide analytical data, and clinicians evaluate it contextually. By training the health professionals in ethics thinking and AI literacy, the technology will be used effectively and responsibly. In essence, Onco-Immuno-Pharmacovigilance is in the future that will enable the harmonisation of data science and compassion, machine precision with clinical intuition to create a new era of predictive and patient-centred oncology safety. Biochemistry, genetics and computational intelligence should be combined in an integrated structure of molecular safety science which is the future of Onco-Immuno-Pharmacovigilance. By incorporating multi-omics biomarkers along with the signatures of enzyme activity and information of genetic polymorphism into AI-based systems, mechanism-based prediction of toxicity rather than post-hoc detection will become feasible. As molecular databases continue to expand and as biochemical assays are standardized, pharmacovigilance will become a biochemically validated genomically directed precision discipline.

CONCLUSION:

Onco-Immuno-Pharmacovigilance development based on AI is a revolutionary step in the history of science of drug safety. The growing complexity of immunotherapy and precision oncology no longer requires the conventional pharmacovigilance systems to identify the type of immune-mediated toxicities that are complex and delayed with the emergence of new therapeutics. Artificial intelligence has now allowed clinicians and researchers to combine various types of data including real-world evidence, multi-omics and electronic health records to create predictive models of drug safety. Machine-learning models can improve the detection of early signals, and explainable artificial intelligence (XAI) systems can promote the credibility and trust of clinicians. This revolution however requires strict data quality and open governance as well as international cooperation. The regulatory bodies all over the world are actively working on implementing AI in the pharmacovigilance process without sacrificing the ethical aspect and privacy of the patients. The final objective is to move towards proactive, patient-specific safety prediction on the basis of reactive surveillance. Onco-Immuno-Pharmacovigilance will be the future of precision drug safety combining both computational intelligence with clinical empathy to make sure that advanced cancer therapies can continue to be life-extending and life-preserving.

DECLARATIONS

AVAILABILITY OF DATA AND MATERIALS:

This article is a review based on previously published data available in public databases and peer-reviewed sources. No new datasets were generated or analysed during this study.

ACKNOWLEDGEMENTS

The authors acknowledge the Department of Pharmacy Practice and the Department of Oncology, Cancer Institute, for continuous academic and clinical guidance.

FUNDING / SUPPORTING AGENCIES

None. This review received no specific grant from any funding agency.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest

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REFERENCES

1. Postow, M. A., Sidlow, R., & Hellmann, M. D. (2018). Immune-related adverse events associated with immune checkpoint blockade. *The New England Journal of Medicine, 378*(2), 158–168.
2. Harpaz, R., DuMouchel, W., LePendu, P., Bauer-Mehren, A., Ryan, P. B., & Shah, N. H. (2017). Data-mining methods for pharmacovigilance. *Clinical Pharmacology & Therapeutics, 101*(6), 112–120.
3. Johnson, D. B., Nebhan, C. A., Moslehi, J. J., & Balko, J. M. (2022). Immune checkpoint inhibitor toxicities: Mechanisms and management. *Nature Reviews Clinical Oncology, 19*(12), 761–779.*
4. Haanen, J. B. A. G., Carbonnel, F., Robert, C., Kerr, K. M., Peters, S., & Larkin, J. (2022). Management of toxicities from immunotherapy: ESMO clinical practice guidelines. *Annals of Oncology, 33*(11), 1217–1230.*
5. Chen, M., Lee, J., & Zhao, Q. (2023). AI applications in pharmacovigilance: Current trends. *Drug Safety, 46*(1), 9–25.*
6. Wang, C. Y., Chen, H. C., & Lin, Y. J. (2024). Machine-learning algorithms for adverse drug event detection in oncology. *Frontiers in Pharmacology, 15*, 1182762.*
7. Sato, K., Nomura, M., Takahashi, H., et al. (2023). Predictive genomics of immunotherapy-induced toxicity. *Journal for ImmunoTherapy of Cancer, 11*(1), e005913.*
8. Topol, E. J. (2019). High-performance medicine: The convergence of human and artificial intelligence. *Nature Medicine, 25*(1), 44–56.*
9. U.S. Food and Drug Administration. (2024). *FDA Sentinel Initiative annual report 2024.*
10. European Medicines Agency. (2025). *DARWIN EU network: Real-world evidence strategy 2025.*
11. Weber, J. S., Yang, J. C., Atkins, M. B., & Disis, M. L. (2015). Toxicities of immunotherapy: Mechanisms, predictive markers, and management. *Cancer Immunology Research, 3*(3), 278–285.*
12. Michot, J. M., Bigenwald, C., Champiat, S., et al. (2016). Immune-related adverse events with immune checkpoint blockade. *European Journal of Cancer, 54*, 139–148.*
13. Neelapu, S. S., Tummala, S., Kebriaei, P., et al. (2018). Chimeric antigen receptor T-cell therapy—Assessment and management of toxicities. *Nature Reviews Clinical Oncology, 15*(1), 47–62.*
14. Shimabukuro-Vornhagen, A., Gödel, P., Subklewe, M., Stemmler, H. J., Schlößer, H. A., Schlaak, M., Kochanek, M., Böll, B., & von

Bergwelt-Baildon, M. (2018). Cytokine release syndrome. *Journal for ImmunoTherapy of Cancer, 6*(1), 56.*
15. Salem, J. E., Allenbach, Y., Vozy, A., et al. (2019). Abatacept for severe immune checkpoint inhibitor–associated myocarditis. *The New England Journal of Medicine, 380*(24), 2377–2379.*
16. Baxi, S., Yang, A., Gennarelli, R. L., et al. (2018). Immune-related adverse events for anti–PD-1 and anti–PD-L1 drugs: Systematic review and meta-analysis. *JAMA Oncology, 4*(2), 216–222.*
17. Liang, J. J., Lee, J., Zhao, Y., et al. (2023). Integrating pharmacogenomics into AI frameworks for cancer immunotherapy safety. *Frontiers in Oncology, 13*, 1094725.*
18. Kotecha, N., Kriegeskorte, N., & Hinton, G. (2023). Data fusion approaches for multimodal learning. *Nature Reviews Genetics, 24*(1), 45–60.*
19. Zhang, X., Zhao, J., Xie, J., et al. (2022). NLP-driven pharmacovigilance using unstructured data. *Drug Safety, 45*(4), 385–397.*
20. Liu, X., Chen, R., Wang, Y., et al. (2023). Deep learning for signal detection in pharmacovigilance databases. *Frontiers in Pharmacology, 14*, 1112349.*
21. Liu, R., Qin, L., He, Y., et al. (2023). Artificial intelligence in pharmacovigilance: Opportunities and challenges. *Frontiers in Pharmacology, 14*, 1121459.*
22. Morita, M., Shimizu, T., Sakurai, K., et al. (2022). Text mining of oncology adverse events using NLP. *International Journal of Medical Informatics, 161*, 104747.*
23. Razzak, M. I., Imran, M., & Xu, G. (2020). Big data analytics for preventive medicine. *Neural Computing and Applications, 32*(15), 10383–10401.*
24. Tan, Y., Wei, J., Fang, J., et al. (2023). Radiomic signatures predicting immune-related adverse events. *Frontiers in Immunology, 14*, 1187791.*
25. Banerjee, I., Ling, Y., Chen, M. C., et al. (2024). Real-time decision support using AI for oncology adverse event management. *JCO Clinical Cancer Informatics, 8*, e2400195.*
26. Singh, N., Verma, R., & Sahu, A. (2023). Federated learning for healthcare data privacy. *BMC Medical Informatics and Decision Making, 23*(1), 65.*
27. Daly, A. K., & Day, C. P. (2019). Genetic association studies in drug-induced liver injury. *Seminars in Liver Disease, 39*(1), 52–61.*
28. Zhernakova, D. V., Klungland, A., & Zhernakova, A. (2022). Epigenetic and genetic interplay in autoimmunity. *Nature Reviews Immunology, 22*(6), 403–417.*
29. Hosoya, N., Kinoshita, A., & Nakamura, Y. (2022). HLA associations with immune-related adverse events. *Cancer Immunology Research, 10*(7), 783–791.*
30. Yoshino, K., Nakayama, T., Ito, A., et al. (2023). HLA-DRB1*11:01 and CTLA4 polymorphisms in immunotherapy-induced hepatitis. Journal of Immunotherapy, 46(3), 125–133.*
31. Lin, J., He, H., Wang, Q., et al. (2023). Cytokine receptor variants associated with immunotherapy-induced cytokine storm. *Frontiers in Immunology, 14*, 1128452.*
32. Chen, Q., Wu, X., Li, M., et al. (2023). AI-based pharmacogenomic modeling for immune toxicity prediction. *Bioinformatics, 39*(5), btad224.*
33. Sato, K., Nomura, M., Takahashi, H., et al. (2023). Predictive genomics of immunotherapy-induced toxicity. *Journal for ImmunoTherapy of Cancer, 11*(1), e005913.*
34. Liang, J. J., Lee, J., Zhao, Y., et al. (2023). Integrating pharmacogenomics into AI frameworks for cancer immunotherapy safety. *Frontiers in Oncology, 13*, 1094725.*
35. Wang, C. Y., Chen, H. C., & Lin, Y. J. (2024). Machine-learning algorithms for adverse drug event detection in oncology. *Frontiers in Pharmacology, 15*, 1182762.*
36. Ghosh, R., Singh, A., & Bandyopadhyay, P. (2023). Translating pharmacogenomics to oncology safety practice. *Frontiers in Pharmacology, 14*, 1139052.*
37. Lee, H., Yoon, H., & Choi, Y. (2024). Explainable artificial intelligence for pharmacogenomics. *Briefings in Bioinformatics, 25*(2), bbad562.*
38. Liao, J., Zhang, X., & Li, H. (2023). Challenges in AI-driven pharmacovigilance. *Drug Safety, 46*(4), 333–345.*
39. Bousquet, C., Grenier, C., & Lillo-Le Louët, A. (2024). Standardizing MedDRA for AI-based safety systems. *Drug Safety, 47*(3), 255–266.*
40. Challen, R., Denny, J., Pitt, M., et al. (2019). Artificial intelligence, bias, and clinical safety. *BMJ, 365*, l1871.*
41. Mehrabi, N., Morstatter, F., Saxena, N., et al. (2021). A survey on bias and fairness in machine learning. *ACM Computing Surveys, 54*(6), 1–35.*
42. Linardatos, P., Papastefanopoulos, V., & Kotsiantis, S. (2023). Explainable AI: Applications in medicine. *Health Informatics Journal, 29*(1), 1460458231177.*
43. European Parliament. (2025). *EU AI Act 2025: Regulation on artificial intelligence.* Publications Office of the European Union.
44. World Health Organization. (2023). *Smart pharmacovigilance initiative report 2023*. Uppsala Monitoring Centre.
45. Indian Pharmacopoeia Commission. (2024). *Pharmacovigilance Programme of India annual summary 2024*.
46. Ministry of AYUSH. (2024). *PPvAYUSH annual report 2024*. Government of India.

47. Bittner, M. I., Mayer, S., & Creutzburg, M. (2023). International collaboration in AI pharmacovigilance. *BMC Medical Informatics and Decision Making, 23*(1), 156.*