Transforming Pharmacovigilance With Pharmacogenomics: Toward Personalized Risk Management

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Pharmacovigilance is a critical component of medication safety. Despite rigorous evaluation of new drugs during clinical trials, some adverse effects might only be identified once pharmaceuticals are used by a larger population for a longer duration. Adverse drug reactions cause negative healthcare outcomes and in severe cases, may lead to hospital admissions, delayed hospital discharges, or deaths. Adverse event reports submitted to pharmacovigilance programs by healthcare professionals and consumers are a key source of information regarding previously unrecognized detrimental effects. Pharmacogenetic markers that indicate how particular genes impact an individual's response to medication can help explain some idiosyncratic adverse reactions. Incorporating pharmacogenomic guidance in prescribing is proven to decrease the incidence of adverse reactions and improve clinical outcomes. However, this information is not yet routinely included in incident reports. In this era of precision medicine, when prescribing can be tailored to the individual, pharmacogenomic test results yield valuable data that can enhance both individual and population health. Furthermore, advanced artificial intelligence (AI) and machine learning (ML) methods facilitate analysis of complex genetic data, revealing insights not previously available. This white paper outlines current pharmacovigilance and pharmacogenomic practices and recommends that pharmacovigilance programs include pharmacogenomics as a crucial data point in their investigations.

Pharmacovigilance (PV) is defined by the World Health Organization (WHO) as the science and activities related to the detection, assessment, understanding, and prevention of adverse effects and other drug-related problems.[1] The WHO-Uppsala Monitoring Centre was established in Sweden in 1978 with the goal of advancing PV efforts globally. Initially a pilot project to foster international collaboration, it evolved into an enriched database (Vigibase)[2] housing millions of adverse drug reaction (ADR) reports submitted by healthcare providers and patients from member nations. Over the past several decades, PV programs have played a key role in enhancing medication safety worldwide, with their findings resulting in critical interventions, including market withdrawals (e.g., rofecoxib, 2004; a nonsteroidal anti-inflammatory drug approved for conditions such as acute pain and inflammation, found to increase risk for heart attack and stroke, particularly with long-term use),[3] mandated boxed warnings (e.g., fluoroquinolones, 2008; approved for infections, e.g., of the respiratory tract or urinary tract, and subsequently noted to be associated with potentially permanent injury of the tendons, muscles, joints, and nerves),[4] and safety-related labeling changes (e.g., lecanemab-irmb, 2025; approved for treatment of Alzheimer's disease, the drug's boxed warning was revised to alert clinicians to the potential for the side effect of neurologic deficits to mimic signs of ischemic stroke and to test for variants in the Apolipoprotien E gene (ApoE) prior to initiating therapy).[3]

Over time, advancements in the field of precision medicine have refined medical practice from a "one-size-fits-all" approach toward "right drug, right dose, right patient." Integral to this updated practice is the inclusion of genetics, ranging from biomarkers of disease to pharmacogenetic indicators of drug effects used to target therapies toward greater efficacy and safety. Pharmacogenomic (PGx) information is increasingly incorporated into drug labeling to enhance patient safety and therapeutic efficacy. Recognizing the increasing prevalence of pharmacogenetic guidance in drug labeling, the FDA launched the Table of Pharmacogenetic Associations in 2020,[5] including 22 distinct drug–gene pairs with data indicating potential impact on safety or response. Additionally, guidelines from collaborations such as the Clinical Pharmacogenomics Implementation Consortium (CPIC)[6] and the Dutch Pharmacogenetics Working Group (DPWG)[7] direct clinicians to optimize prescriptions based

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on their patient's pharmacogenomic markers. In addition, drug labeling increasingly incorporates pharmacogenomic information to enhance patient safety and therapeutic efficacy. Clopidogrel, an anti-platelet medication used to prevent blood clots in people at risk for heart attack or stroke, provides a notable example. In 2013, the FDA approved the drug label for clopidogrel (Plavix®) warning that patients who are CYP2C19 poor metabolizers may have diminished effectiveness of the drug and advising healthcare providers to consider alternative treatments for impacted individuals.[8] Such label updates highlight the importance of PGx in precision medicine.

As genetic technology and accessibility continue to evolve, so too has the capability of AI/ML to search, detect, and analyze signals in large, complex data sets. These models can be trained to support highly complex genetic data, improving identification of ADRs linked to specific genotypes. As our understanding of genetic contributors to ADRs grows, PV efforts can be increasingly tailored toward specific patient cohorts, potentially resulting in more individualized risk management strategies.

BASIC PRINCIPLES

Adverse drug reactions

The WHO defines an ADR as "a response to a medicine which is noxious and unintended, and which occurs at doses normally used in man." ADRs pose a significant public health risk, contributing to mortality and hospitalizations. One landmark study estimated serious ADRs to rank as high as the fourth leading cause of death among hospitalized patients in the United States (U.S.).[8] Less serious ADRs do not result in hospitalizations or death but still may significantly impact a patient's health.[9] Effective prevention strategies are essential to reducing the number and severity of these potential negative outcomes.

ADRs were initially classified into two types: Type A (dose-related) and Type B (non-dose-related) before the classification system expanded to six to account for additional clinical scenarios.[10] For the purposes of this review, we will focus on the original two types (**Table 1**). Type A reactions are the most common, accounting for 85–90% of all ADRs.[11] These reactions are usually dose-dependent and predictable based on the known pharmacology of the drug. In contrast, Type B reactions are inherently unpredictable. They do not follow a simple dose–response relationship and may occur in only a small subset of patients.[12]

It is important to emphasize that ADRs differ from medication errors in that they arise despite correct prescription, proper administration, and good adherence. Notably, systematic procedural changes and error-prevention processes for drug delivery systems that improve drug safety by mitigating medication errors may not address ADRs.[13] Pharmacovigilance systems, on the other hand, are commonly used to prevent ADRs through detection and reporting.[14]

Table 1 Type A and Type B ADRs, adapted[11]

Reaction description and type[a]	Details
Drug overdoses [A]	Excessive drug intake, e.g., liver failure with acetaminophen overdose. Side Effects: Undesirable effects unrelated to the drug's primary purpose, e.g., gastritis with nonsteroidal anti-inflammatory drugs (NSAIDs)
Drug interactions [A]	Reactions due to interaction with other substances, e.g., reduced anticoagulant effects of warfarin with increased vitamin K intake
Hypersensitivity reactions [B]	Immune-mediated responses classified into Types I–IV, ranging from immediate (e.g., anaphylaxis) to delayed (e.g., Stevens-Johnson syndrome) Other Immunological Reactions: Autoimmune disorders (e.g., lupus-like syndrome) or fixed drug eruptions
Idiosyncratic reactions [B]	Rare reactions linked to genetic factors, such as hemolysis in glucose-6-phosphate dehydrogenase (G6PD) deficiency
Pseudo allergic reactions [B]	Resembling allergic reactions but non-immunologic, e.g., vancomycin flushing syndrome

[a]While these classifications help in understanding and managing ADRs, overlapping symptoms can occasionally complicate differentiation between types.

PHARMACOVIGILANCE CONCEPTS

Development of pharmacovigilance

The need for PV became evident in the 1950s following widespread birth defects caused by thalidomide use during pregnancy. This tragedy ultimately led to the enactment of the Kefauver–Harris Act of 1962, which granted the FDA greater oversight of drug safety.[15] The FDA then mandated manufacturers to report ADRs.[16,17] In 1993, the FDA established MedWatch, a program allowing voluntary reporting of ADRs by healthcare professionals and the public.[18] Data from MedWatch and pharmaceutical companies are compiled in FAERS, which supports safety monitoring and transparency through resources such as the FAERS Public Dashboard—for example, tracking ADRs related to COVID-19 therapies.[19,20]

As PV specifically aims to improve medication safety, patient care, and public health,[21] it spans the life cycle of the drug development process, beginning in preclinical research and extending into post-marketing settings. In the United States, the FDA mandates PV efforts in both the pre- and post-marketing phases.[14] Although pre-marketing PV during clinical trials may contribute to the detection of ADRs, these trials are limited by relatively small sample sizes, strict inclusion/exclusion criteria, and short durations. Consequently, certain ADRs may only become evident after prolonged use of drugs in heterogeneous, real-world populations. Thus, post-marketing surveillance serves as a vital component of PV.[22]

High-quality reporting is critical for effective PV. The clinical data collection process for PV begins with gathering individual case safety reports (ICSRs), which can originate from either solicited or unsolicited sources (**Figure 1**). An ICSR is defined as "a description of an adverse event / adverse drug reaction or other observation in an individual patient at a specific point in time."[23] Solicited reports are gathered by organizations actively requesting information from patients or study participants at

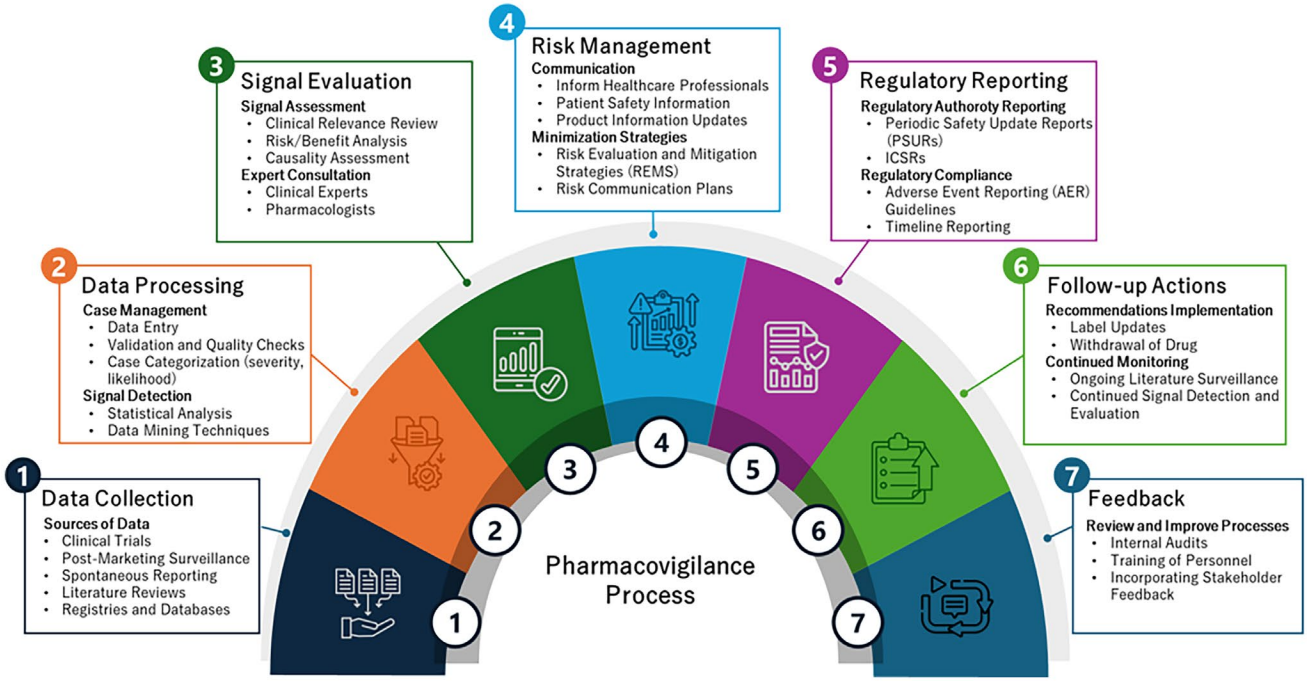

Figure 1 The pharmacovigilance process.

structured timepoints (e.g., clinical trials, post-marketing surveillance). Unsolicited reports are gathered by organizations passively where the patient taking the drug or their healthcare professional provides the information without a request at spontaneous timepoints dictated by when the ADR occurs (e.g., reporting systems such as MedWatch).[24] Once collected, ICSRs are stored in databases maintained by the collecting organization such as the FDA Adverse Event Reporting System (FAERS) in the United States and EudraVigilance in Europe.[14,25] In the United States, the FDA outlines "Good Pharmacovigilance Practices," emphasizing characteristics of a quality case report, such as detailed clinical descriptions and timelines (**Table 2**). The FDA's guidance for industry on PV planning underscores the importance of genetic testing in identifying patient subpopulations at higher risk for ADRs. It directs that safety specifications should include data on "sub-populations carrying known and relevant genetic polymorphism," as genetic testing can provide critical insights into susceptibility to adverse reactions.[26] Internationally, organizations such as the European Medicines Agency (EMA) and the WHO have implemented similar pharmacovigilance frameworks to promote global drug safety.[27,28]

Globally, the WHO's VigiBase serves as the largest repository of ICSRs, encompassing reports from more than 170 countries.[30] These reporting mechanisms are instrumental in identifying emerging safety concerns and guiding subsequent investigations (**Figure 1**). Outcomes from such efforts may include withdrawal of drugs, as exemplified by sibutramine (FDA-approved for weight loss in 1997, withdrawn from the market in 2010 following evidence of increased risk for major adverse cardiovascular events),[31] label updates to include black box warnings as well as warnings and precautions, as seen with natalizumab (FDA-approved for multiple

Table 2 Characteristics of a good case report. Adapted from: U.S. Food and Drug Administration (FDA). Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment. Silver Springs, MD: FDA, 2018[29]

Element	Additional details
Description of the adverse events or disease experience	Time to onset of signs or symptoms
Suspected and concomitant product therapy details	Dose, lot number, schedule, dates, duration, concomitant products including over-the-counter medications, dietary supplements, and recently discontinued medications
Patient characteristics	Demographic information (e.g., age, race, sex), baseline medical condition prior to product therapy, co-morbid conditions, use of concomitant medications, relevant family history of disease, and presence of other risk factors
Documentation of the diagnosis of the events	Methods used to make the diagnosis
Clinical course of the event and patient outcomes	Hospitalization, death etc.
Relevant therapeutic measures and laboratory data	At baseline, during therapy, and after therapy, including blood levels, as appropriate
Dechallenge and/or rechallenge	Information about patient response
Any other relevant information	Other details relating to the event or information on benefits received by the patient, if important to the assessment of the event

sclerosis in 2024, temporarily withdrawn in Feb 2005 following 2 cases of a serious brain disease, progressive multifocal leukoencephalopathy),[32] and updates to dose limitations, such as the restriction of 80 mg simvastatin due to myopathy risks (FDA-approved for hyperlipidemia in 1991, subsequently noted to increase risk for skeletal muscle weakness, stiffness, and pain).[33]

THE CURRENT PHARMACOVIGILANCE LANDSCAPE

The current PV landscape reflects a multifaceted approach to ensuring drug safety. Data collection sources include ICSRs submitted by healthcare professionals to regulatory authorities,[34] ADR case reports in medical literature,[35] pharmacoepidemiologic studies, and observational databases such as electronic health records (EHRs).[36] AI and ML offer potential for enhanced signal detection and analysis, yet challenges remain in data quality and integration.[37]

Key FDA resources, such as drug labels and Table of Pharmacogenetic Associations, exemplify PV efforts to educate stakeholders and optimize drug use beyond addressing ADR reports.[38] Tangible impacts include improved safety warnings, label changes, and Risk Evaluation and Mitigation Strategies (REMS), underscoring PV's role in advancing precision medicine by matching drugs to appropriate patient populations.[39]

Globally, PV programs are at different stages of development. While developed countries prioritize extensive post-market surveillance, others are still expanding their infrastructure to include mandatory reporting, regulatory support, and surveillance mechanisms.[40] These differences influence signal detection and the incorporation of PGx insights.[41] International efforts by organizations such as the International Society of Pharmacovigilance and the American Society of Pharmacovigilance aim to integrate PGx into PV practices, addressing gaps in global data collection and application.[42]

Despite progress, limitations persist, such as underreporting, reliance on voluntary submissions, and inconsistent data standards across jurisdictions. These disparities can obscure or delay the detection of pharmacogenomic safety signals, particularly when rare genetic variants or population-specific allele frequencies are involved. In regions with limited infrastructure, genetic data may be absent altogether, while in others, variations in case reporting thresholds or coding systems can hinder data aggregation. Such heterogeneity challenges the generalizability and reproducibility of PGx-based safety signals. Addressing these gaps requires harmonized global efforts, including standardized adverse event reporting systems, broader adoption of structured genomic data in regulatory submissions, and the use of advanced analytics to reconcile cross-border data variability.[42]

THE CURRENT PHARMACOGENOMICS LANDSCAPE

Pharmacogenomics is the science and clinical practice of using patient genetic data to improve drug safety and efficacy. More than 95% of patients have been found to have an actionable pharmacogenetic variant that would change treatment.[43–46] In reality, it is likely that every patient has a pertinent pharmacogenetic variant, though we do not yet have genetic information available in every patient, nor has the scientific community discovered all important PGx variants. Increasing specificity of polygenic risk scores will certainly leverage smaller impact genetic variants together, further improving the predictability of drug response. Availability of PGx data is becoming more widespread in clinical practice, with test results now available through multiple sources. Several major health organizations in the United States now have a PGx program.[47,48] Moreover, the FDA has approved direct-to-consumer testing that provides results that can be used to change prescribing. These tests have increased patient awareness and interest in PGx. For example, 23andMe, with almost 13 million people genotyped, has developed more than 55 reports that meet FDA requirements.[49,50] Thus, PGx results should be assessed if available, or ordered if not, when considering the etiology of adverse drug events.

Genetic determinants of pharmacokinetics and pharmacodynamics are increasingly understood by researchers and clinicians, as evidenced by the > 23,000 drug/gene-variant annotations curated in the ClinPGx knowledgebase. Importantly, over the past decade, the CPIC (www.cpicpgx.org) has published 28 peer-reviewed guidelines and 17 updates involving 160 drugs and 34 genes to facilitate the translation of pharmacogenomic data into actionable prescribing algorithms.[51] The US Department of Veterans Affairs uses these data extensively through its Pharmacogenomics testing for veterans program (PHASER)[52,53] and several major health insurance carriers, including Medicare, cover PGx testing. Further, the US FDA Division of Translational and Precision Medicine maintains a growing list of PGx biomarkers in drug labeling that contains 541 drugs as of January 2025.[54] Genetic variability is now assessed as part of the new drug approval process,[55] with PGx data used to maximize efficacy and minimize adverse drug events (ADEs).

PROPOSAL FOR INCORPORATION OF PGx INTO PV PROGRAMS

Although PGx is both evidence-based and guideline-supported, it is not yet routinely implemented in PV programs. Several novel research studies outline successful approaches to including PGx in PV analysis. The following three studies provide distinct approaches, highlighting the feasibility of this goal:

- A 2003 study by Aronson and Ferner proposed a new framework for ADR classification, emphasizing the integration of pharmacogenetic (PGx) data into PV practices. The three-dimensional system, known as DoTS (Dose-Time-Susceptibility), classified ADRs based on dose dependence, timing, and patient susceptibility. By incorporating PGx insights into the susceptibility dimension, the framework highlighted how genetic polymorphisms, such as those affecting cytochrome P450 enzymes or drug transporters, could influence individual responses to medications. This approach bridged gaps in traditional ADR classification systems, which often failed to account for patient-specific factors. The DoTS system enabled personalized PV by identifying high-risk populations and providing mechanistic insights into ADRs. This integration of PGx data guided drug monitoring strategies, informed clinical decisions, and supported the development of tailored therapies. By addressing individual variability in ADR risk, this framework enhanced PV's

predictive and preventive capabilities, paving the way for safer, more effective, and personalized drug use.[56]

- A 2004 study by Clark *et al*. introduced a novel methodology for integrating pharmacogenetics (PGx) into PV by linking genetic research with prescription event monitoring (PEM) studies. It highlighted the potential of PGx to identify genetic factors, such as variations in P-glycoprotein (P-gp) and CYP2C9, that contributed to individual susceptibility to ADRs. Using minimally invasive buccal swabs for DNA collection and a nested case–control study design, the research demonstrated the feasibility of investigating genetic risks for ADRs in real-world settings. While the pilot study had limited statistical power, it set the stage for larger scale, population-based research, particularly in diverse genetic cohorts, to refine the role of PGx in ADR prevention. Ultimately, this integration of PGx into pharmacovigilance offered a powerful tool for enhancing drug safety, developing guidelines for pre-treatment genotyping, and ensuring more effective and precision medication use.[57]
- A 2008 study by Koh *et al*. introduced a quantitative solution for assessing ADR causality using a genetic algorithm to optimize scoring criteria, providing precise probability scores for ADR likelihood. Tested on cases from Singapore's PV center, the algorithm achieved high sensitivity (83.8%) and specificity (71.0%), outperforming conventional methods. It offered a robust, objective tool for differentiating true ADR signals from noise, particularly in settings with limited data or unprecedented ADRs, such as clinical trials. The algorithm enhanced inter- and intra-rater agreement, aiding clinicians, regulatory agencies, and pharmaceutical companies in ADR prediction and management. Its adaptability for incorporating new data makes it a valuable addition to PV systems, with potential future integration of pharmacogenetic data to address genetic variability in ADR susceptibility.[58]

While these studies involved limited populations, they all identified opportunities for future research and expansion. Building on this research, we propose incorporating PGx into PV in three key areas:

- Data input and collection,
- Data analysis and risk evaluation,
- Data output and action.

Data input and collection

Current state. PV data come from various sources, including spontaneous reporting systems such as FAERS, pharmaceutical company reports, clinical trials, literature, and collaborations with biobanks.

Patients and healthcare providers use tools such as FDA Form 3500 (healthcare providers) or Form 3500B (consumers) to report ADRs and interactions with pharmaceutical manufacturer representatives to share essential details about the event, the drug, and the patient.

Most PV data are collected by pharmaceutical companies, which generate ICSRs and initiate PV activities through internal teams or outsourced vendors. ICSRs are a vital source of post-marketing drug safety data. As of March 2025, FAERS had received more than 30 million reports, of which almost 17 million were serious reports and almost 3 million were death reports.[19] The FAERS database contains both structured and unstructured data; structured data regarding ADRs are coded with a uniform vocabulary (MedDRA, developed by the International Conference on Harmonization of Technical Requirements for Pharmaceuticals for Human use, ICH) to facilitate data search and analysis. Utilization of standardized coding terminology also allows for collation of data from various international databases. Specific unstructured data may be coded by MedDRA and added to structured data fields.[59] These data are, however, associated with limitations, for example, reporting is voluntary, so not all events are captured. Therefore, it is not possible to calculate the incidence or prevalence of an ADR from PV data alone. Furthermore, reports may be incomplete or even duplicated. Reporting ratios of the adverse event reports vs. estimated drug utilization may be considered an estimation of the adverse event, but it is not an accurate representation of the true event rate.[60]

Clinical trials also contribute significantly to PV efforts, exemplified by the identification of genetic associations such as HLA-B*5701 for abacavir (an antiviral drug, approved for the treatment of HIV) and HLA-B*5801 for carbamazepine (FDA-approved for seizure, bipolar disorder, and neuropathic pain).[61]

EMA mandates the inclusion of PGx considerations in Risk Management Plans (RMPs), requiring genomic data collection and monitoring during both clinical trials and the post-authorization phase. This ensures the integration of genetic factors into drug safety assessments, addressing variability in patient responses.[62]

Literature sources, including case reports and pharmacoepidemiologic studies, further enhance PV by identifying rare or idiosyncratic reactions and uncovering patterns in drug use and outcomes across larger populations.[63] To ensure quality case reports, authors should follow the 13-point checklist outlined by the CARE case report guidelines.[64] Developed by international experts, these guidelines promote the accuracy, transparency, and usefulness of case reports.

Databases such as ClinPGx, which curate information on the impact of genetic variation on drug response, are invaluable resources for integrating PGx into PV. ClinPGx provides summaries of gene-drug relationships, genotype–phenotype associations, and clinical guidelines, helping PV systems identify genetic factors in ADRs and recommend appropriate PGx testing. For instance, if an ADR with a known genetic association is reported, ClinPGx can guide the selection of relevant genes or variants to investigate.[65]

Incorporating pharmacogenomics. Enhancing PGx integration into PV processes could be achieved by modifying FDA Form 3500/3500B to include a dedicated field for PGx information, such as genetic test results, genotype/phenotype details, or whether PGx testing has been conducted. The current form does not have any fields specifically for PGx; therefore, any PGx data collected thus far are gathered from free-text fields including descriptions/commentary and laboratory data. Adding prompts like, "Has PGx testing been performed for this patient? If not, consider a PGx test for drugs with known genetic associations," would encourage

systematic collection of genetic data. For example, in cases of clopidogrel-related stent thrombosis, PGx testing could identify at-risk individuals with genetic variants affecting drug response, enabling improved RMPs and patient safety.

The EMA stresses systematic genomic biospecimen collection and signal detection for serious ADRs or unexpected drug responses. This approach supports continuous evaluation of genetic factors in real-world settings, ensuring pharmacogenomic insights remain central to ADR prevention and management.[62] Genetic differences across populations further highlight the need for PGx data in PV systems. For example, G6PD deficiency, prevalent in African and Mediterranean populations, illustrates the importance of considering ethnicity in PV workflows. Incorporating such data enables improved ADR stratification by ethnic subpopulations, allowing targeted safety monitoring and reducing health disparities.[66]

Soliciting additional data to understand ADR risk factors are a key aspect of PV. PGx testing is particularly useful for identifying genetic variants linked to drug responses, especially comprehensive panel testing. PGx panel testing may be warranted when genetic factors are suspected, supported by evidence or emerging patterns. PV systems, designed to detect rare outcomes like drug-induced liver injury (DILI), can benefit from including genetic insights alongside additional confounding factors such as phenoconversion and drug–drug interactions.

Dynamic PV frameworks are required to address the challenges of transient changes in metabolic phenotypes due to drug interactions or conditions such as inflammation. These temporary alterations can impact genotype–phenotype concordance, underscoring the importance of real-time data collection and integration into PV systems. For instance, a patient's phenotype may temporarily shift due to inflammation, affecting drug metabolism and potentially masking or exacerbating ADR signals. Such scenarios necessitate flexible PV systems capable of adapting to dynamic patient conditions.[67]

Pharmacovigilance data often lead to the categorization of extreme phenotypes, such as ultra-rapid metabolizers (UMs) or poor metabolizers (PMs). PGx data enhance population-level analyses of these rare phenotypes, enabling comparisons of ADR rates with background allele frequencies by ethnicity. This approach helps refine drug labeling and mitigate risks. Incorporating both genotype and phenotype data in PV reporting supports comprehensive risk assessments and improves understanding of genetic contributions to drug safety.

In addition to FAERS and ICSRs, PV data are derived from collaborations with biobanks, case studies, and consortiums, which provide opportunities to identify rare genetic variants and refine safety profiles. By integrating PGx considerations into ADR reporting, ICSRs, and clinical trial protocols, pharmaceutical companies can improve the prediction, prevention, and management of ADRs (**Figure 2**). This integration not only advances precision medicine while aligning with regulatory expectations but also enhances patient safety by leveraging genetic insights to mitigate risks effectively.

Data analysis and risk evaluation

Data availability. While PGx data have become more available, not all patients are genotyped. PGx tests can and should be recommended as part of a causal assessment when data support clinical implementation. Patients can request such testing, which is increasingly reimbursed by insurers, but may not realize they already have access to these data through direct-to-consumer (DTC) providers. Thus, both patients and their treating clinicians must be queried about the availability of these results through clinical laboratories or DTC providers. Patients may be referred for testing when the clinical case suggests the need for these results.

Adequacy of genotyping. To ensure accurate results, a PGx test must cover all relevant genetic variants. The PGx community has only recently begun to specify which variants are necessary to claim adequate coverage of a gene.[68,69] Full sequencing with adequate phasing to capture variation on both DNA strands provides the most complete picture of a patient's genome.[70] This technique is infrequently performed in clinical practice due to concerns about the cost and resources required for interpretation and data storage. The sequence data for an entire genome requires approximately 150 gigabytes of storage space, meaning exabytes of data storage with robust deidentification security measures are required to store these data on a population level. However, leading companies, such as Illumina and PacBio,[71] are making these data more available and whole genomic sequencing cost has decreased to as low as $100.[72]

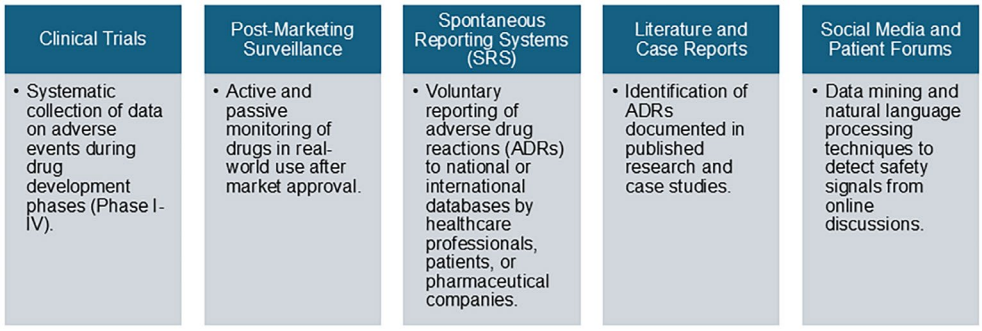

Figure 2 Sources and processes for pharmacovigilance data generation. PV data are generated through a variety of sources and processes aimed at monitoring the safety and efficacy of medicines and detecting adverse drug reactions (ADRs).

As a cost-effective alternative to full sequencing, most clinical laboratories now utilize microarray platforms that allow capture of a large number of single nucleotide variants (SNVs). With these tests, each individual base pair variant can be stored in a discrete data field, which requires minimal storage and facilitates assessment, accurate interpretation, and discovery when new clinical phenotype patterns emerge. When paired with long-range reads, this technique can capture a large amount of genomic variability with adequate coverage of common clinically actionable variants. The Association for Molecular Pathology, College of American Pathologists, Dutch Pharmacogenetics Working Group of the Royal Dutch Pharmacists Association, and European Society for Pharmacogenomics and Personalized Therapy provide excellent resources with a list of minimum variants that must be captured when considering whether a test is sufficient for clinical interpretation.[73] Assessment of the variants covered by the test provider is necessary to prevent misclassification of predicted phenotypes and false attribution when patients are insufficiently genotyped.

Pharmacovigilance signal strength. The goal of data screening is to identify new safety signals, which suggest causal associations between the drug and the adverse event. While every ICSR cannot be individually screened, complementary approaches are employed for more efficient signal identification. FDA then categorizes the causality as either *probable, possible, unassessable*, or *unlikely*.[74] Data mining typically relies on disproportionality analysis to identify drug and adverse event pairs that occur more frequently than other combinations in the database.[74] Extreme discordant phenotypes[75] that result in severe ADRs are most likely to result in the identification of PGx associations. Initial integration should focus on analyzing available genetic data first, then genotyping patients with these severe ADRs when genotype data are not available. Combining data across PV providers will be necessary for low-frequency genetic variants and less common race/ethnicities. Signal strength can also be increased through the distillation of variants into predicted phenotypes. There must be a pipeline to provide phenotypic prediction based on the genetic variants assessed. Furthermore, robust analysis of the impact of PGx results incorporated into ICSR reports would necessitate comparison with population allele frequencies already cataloged in PGx databases such as ClinPGx.[76] This approach is already documented via published case studies outlining rare variants linked with adverse drug reactions.[77]

Data output and action

A comprehensive PV program should encompass both risk identification and risk mitigation strategies to ensure drug safety and efficacy. Risk identification involves the detection of ADRs and potential PGx associations, while risk mitigation includes implementing appropriate strategies, such as preemptive testing, targeted prescribing, and updating product information. When an ADR is reported, the PV process involves assessing the event, submitting a detailed report to regulatory authorities such as the FDA or the EMA, and developing a targeted risk mitigation strategy. If a PGx link is identified, risk mitigation should focus on developing preemptive testing strategies and tailoring recommendations to target populations.[55] For example, in severe reactions such as Stevens–Johnson Syndrome (SJS), the question arises whether routine preemptive HLA testing should be performed in all patients at risk.

To improve the integration of PGx data into PV, ADR reporting forms should include fields for PGx information. This could involve leveraging existing lab result fields or introducing a specific PGx section to capture genetic test results, genotype/phenotype details, or patient testing history. During the initial ADR report or follow-up investigations, healthcare providers or pharmacists managing the PV process should query whether PGx testing has been performed or if the patient is willing to submit to testing. The FDA—or equivalent regulatory agency, as applicable—could recommend *post hoc* PGx testing for specific cases, ensuring ADR investigations are thorough and evidence based.

Over time, a PGx-enriched PV database (or biobank) could be developed, incorporating PGx samples from patients with idiosyncratic drug reactions. This database would enable comparison of genetic profiles between patients who experience ADRs and those who do not, potentially identifying new causative genes or genetic markers. Such data could be mined for research purposes, aiding in the discovery of novel PGx associations and enhancing risk stratification strategies.[78]

Effective risk mitigation plans could include product label updates with PGx information, recommendations for genetic testing (mandatory or optional), dosing modifications, or warnings for at-risk populations. For example, if a PGx link suggests a dosing adjustment for poor metabolizers, this information should be clearly communicated to healthcare providers, regulatory bodies, and potentially consumers to improve safety and decision making.

LEVERAGING AI/ML

As more PGx data become integrated into PV systems, advanced tools such as data mining and AI have the potential to significantly enhance safety signal detection, risk factor identification, and patient stratification based on genetic risk profiles. Recent advancements in ML, particularly in natural language processing (NLP) and deep learning, offer promising approaches to analyze the vast and heterogeneous datasets involved in PV. For instance, NLP can efficiently process unstructured data, such as electronic health records (EHRs), case reports, and social media posts, extracting key insights about ADRs and gene-drug interactions. A recent scoping review by Golder *et al*.[35] identified the growing application of NLP and ML in extracting actionable pharmacogenomic information from clinical text to support adverse event detection, particularly in unstructured EHR-linked datasets.

Moreover, ML models, such as Bayesian Confidence Propagation Neural Networks (BCPNNs) and modern deep learning architectures (e.g., transformer-based models), can identify complex patterns in safety data, such as ADR clusters, by incorporating genetic and phenotypic features.[79] For example, Bayesian Confidence Propagation Neural Networks have been successfully used in spontaneous reporting databases to detect subtle PGx-associated safety signals that might be overlooked using traditional disproportionality analysis.[80] These tools have been shown to support the identification of rare, PGx-related adverse events, such as SJS linked

to HLA-B*1502 or drug-induced hepatotoxicity associated with CYP polymorphisms, by enhancing sensitivity in signal detection frameworks.[79] Another recent study used a novel message-passing neural network model that integrates drug–gene expression and structural data to accurately predict drug–adverse reaction associations, offering a cost-effective approach to enhance drug safety assessments.[81]

Integrating PGx into PV workflows enables personalized safety monitoring by identifying populations at heightened genetic risk for ADRs. PGx-guided ML models can incorporate genetic variations affecting drug metabolism—such as CYP2D6, CYP2C19, or SLCO1B1 polymorphisms—to refine safety signal detection and stratify patients based on susceptibility to specific ADRs. In addition to EHR and claims data, AI/ML systems can link PGx data to real-world safety events from post-market surveillance databases, facilitating proactive identification of high-risk patients and more nuanced benefit–risk assessments.[82] Leveraging advanced algorithms and external data sources, such as molecular structures, geographical reporting trends, and longitudinal health data, enables the detection of subtle safety signals and stratifies patients with greater precision.[83]

The integration of PGx data into PV systems also enhances the utility of real-world data (RWD). AI/ML algorithms can process PGx data alongside RWD from diverse sources—such as EHRs, insurance claims, and patient-reported outcomes—to identify patterns of ADRs that traditional methods may overlook. These systems can refine risk predictions by accounting for genetic factors, environmental influences, and drug–drug interactions, thereby supporting precision medicine approaches in drug safety monitoring. Additionally, causal inference techniques can establish robust links between genetic predispositions and observed ADRs, ensuring actionable insights for clinical decision making.[84]

Emerging digital tools, such as mobile apps and sensors, are increasingly used to collect safety data closer to the point of care. AI/ML models can process these rich data streams to monitor medication adherence, genetic markers, and associated ADRs in real time, improving the scalability and accuracy of PGx-based PV systems. Mobile apps, such as the WEB-RADR App, allow patients to report adverse drug reactions directly, improving the timeliness and quality of safety data. Wearable electrochemical sensors can noninvasively monitor drug levels and physiological parameters in real time, while AI-supported web applications help reduce polypharmacy-related side effects in geriatric patients. The AiRDRUG Web App, for example, supports rational drug use by analyzing drug interactions and patient-specific data to flag high-risk combinations. These tools enhance PV by capturing safety data closer to the point of care.

Governance and regulatory alignment remain critical challenges in realizing the full potential of AI/ML for PGx-enriched PV. Adopting Good Machine Learning Practices (GMLP) and establishing frameworks for data transparency, standardization, and reproducibility will help address concerns about explainability and accountability in ML-driven PGx PV systems. By ensuring regulatory compliance and fostering stakeholder trust, AI/ML systems can drive the adoption of PGx-informed safety monitoring and risk mitigation strategies.[85]

CHALLENGES AND CONTROVERSIES

Despite its critical role in drug safety, PV faces numerous challenges, particularly in the integration of PGx into its framework. The inclusion of PGx data in PV holds promise for improving drug safety and efficacy, yet several uncertainties must be addressed to achieve its full potential. Specific challenges include:

Education and awareness: Many clinicians are unfamiliar with how to interpret PGx data and its clinical relevance, resulting in low uptake and utilization, particularly in regions with limited healthcare resources.[86] Increasing awareness through targeted education programs and integrating PGx knowledge into medical curricula is essential to foster widespread adoption.

Limited availability and utilization of PGx data in PV systems: Current PV frameworks often lack standardized processes for collecting, storing, and analyzing PGx information. The absence of specific fields for PGx data in ADR reports limits its integration into safety signal detection and risk management strategies.[87] Moreover, the lack of prospective clinical trial data demonstrating the clinical and economic value of PGx in optimizing drug dosing and treatment outcomes creates barriers to broader implementation and insurance coverage.[88]

Gene effect size: Effective size and predictive value metrics, such as positive predictive value (PPV), remain inadequately explored for many PGx variants. This gap hinders the ability to robustly correlate PGx data with ADRs, making it difficult to derive actionable insights.[89]

Laboratory standardization: Uniform phenotype calls, robust tests, and the inclusion of all clinically actionable genes with CPIC level A/B evidence and Tier 1/2 alleles are crucial for reliable PGx data generation.[90]

High dimensionality of genomic information: Data complexity impacts the storage, analysis, and mining of PGx data for safety signal detection. Incorporating PGx into PV requires advanced data-sharing frameworks and collaborative initiatives to build large, diverse datasets that can be used to identify safety signals. AI and ML tools, which the FDA has already begun employing for traditional data, must evolve to handle the complexity of PGx data. These tools could revolutionize signal detection by uncovering previously undetected PGx-associated risks.[82]

Ethical, legal, and social implications (ELSI): Privacy concerns surrounding PGx data, particularly regarding data sharing and cybersecurity, pose barriers to its widespread use in PV.[91] In particular, the reuse of PGx data in post-market PV raises questions about informed consent—especially when such data are used retrospectively for purposes not originally disclosed to patients. Informed consent frameworks must be revisited to address the secondary use of data, ensuring transparency, patient autonomy, and compliance with evolving legal standards. Addressing these concerns through robust data protection protocols and clear regulatory guidelines will be essential to building trust among stakeholders. The growing use of biobanking and large-scale genomic integration into PV systems also amplifies these concerns, requiring strict governance mechanisms for data access, usage, and long-term storage.

Engagement with healthcare providers and patients: Providers must understand the value of PGx in enhancing drug safety, while patients should be empowered to participate in PGx testing and

Suggested modifications for consideration in PV programs to include PGx data:

- Update case report forms (e.g., FDA Form 3500) to include a specific field for PGx test results.
- Add prompts to the case report forms to query whether PGx testing has been completed.
- If PGx test results are not available, query whether the patient is willing/able to undergo testing if the drug has an associated PGx recommendation.
- Establish a methodology to confirm assigned phenotypes based on reported genotypes and other dynamic conditions such as drug–gene interactions and phenoconversion.
- Develop an enriched biobank over time, which will facilitate identification of pharmacogenetic factors predisposing to increased risk of ADRs.
- Mine the biobank to identify additional at-risk populations for targeted testing to preempt ADRs.

share data for PV purposes. Meaningful engagement hinges on culturally sensitive communication strategies that respect diverse perspectives on genetic testing and data sharing. This includes transparent discussions about benefits, risks, and data stewardship responsibilities.[92]

CONCLUSION

PGx is emerging as a critical component of comprehensive analysis of ADRs. An abundance of resources supports the use of PGx, ranging from clinical guidelines and primary literature to guidance from drug regulatory agencies. With increasing testing and data availability, PV programs now have both the opportunity and responsibility to include vital patient-specific data in the investigation of ADRs.

To date, several research studies have highlighted the benefit of including PGx parameters in such investigations and outlined methodologies to successfully incorporate this data into PV programs. Furthermore, with rapid advances in AI's ability to analyze complex data, it is now feasible for PV programs to incorporate PGx pharmacogenomics into the process. As data accumulates, these PGx-enriched databases may yield ADR signals that will help inform healthcare providers and pharmaceutical manufacturers to prevent future adverse events.

Studies consistently demonstrate that the vast majority of the population carries at least one clinically actionable pharmacogenetic variant.[43] As awareness of patient heterogeneity and interindividual differences in drug response has evolved over time, so too has our duty to investigate pharmacogenetic factors contributing to ADRs. While we acknowledge challenges to integration, we propose that PV programs solicit pharmacogenomic data as standard practice so that ADRs can be analyzed in the context of possible genetic links. Regulatory bodies can then make precision medicine-directed recommendations or updates based on the findings. In addition to addressing individual ICSRs, aggregating and analyzing PGx data in PV biobanks will prompt the future discovery of novel pharmacogenetic biomarkers for the benefit of the greater population.

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CONFLICTS OF INTEREST

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