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Review on application and development of pharmacogenomics of adverse drug reactions

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ABSTRACT

Adverse drug reactions (ADRs) are a significant public health issue, contributing substantially to patient morbidity and mortality. The growing accessibility of genomic technologies has greatly advanced our understanding of the genetics underlying ADRs. Pharmacogenomics, which investigates how genetic polymorphisms influence individual responses to drug therapy on a genome-wide scale, plays a pivotal role in this field. The article summarizes the relationship between ADRs and genes, outlines the current applications and advancements of pharmacogenomics in the prediction, diagnosis, prevention, regulation, and personalized treatment of ADRs, and reviews cutting-edge research methods and large-scale international studies. These insights aim to provide a reference for the future development of pharmacogenomics in ADR research.

1. Introduction

According to the World Health Organization (WHO),[1] ADRs are harmful and unintended responses to drugs administered at normal doses for the prevention, diagnosis, or treatment of diseases, or for the modification of physiological functions. With the rapid development of drug discovery and the increasing collection of information on drug reactions, it has been found that approximately half of drug-related injuries are caused by potentially preventable ADRs.[2,3] ADRs result in significant economic losses, have a major impact on morbidity and mortality, and pose a serious threat to public health and safety.[4]

In the European Union, ADRs are responsible for up to 197,000 deaths annually, imposing an estimated societal cost of approximately €79 billion each year.[5] It is estimated that ADRs account for 5% of hospital admissions overall, rising to 23% among elderly patients.[6] Adverse reactions are also estimated to rank as the fourth to sixth leading cause of death in the United States. In China, 2.419 million spontaneous ADR reports were submitted nationwide in 2023, and from 1999 to 2023, the national ADR monitoring network accumulated 23.275 million reports.[7] ADRs have become one of the major challenges in clinical practice.

ADRs are influenced by various macro-level factors, such as polypharmacy, inappropriate prescribing, age, and the type of prescription drugs. For instance, drug-drug interactions (DDIs) due to polypharmacy account for 30% of all ADRs.[8] While many ADRs are preventable and often attributed to human error, others appear to be more specific.[9,10] Increasing evidence suggests that genetic differences between individuals, a micro-level factor, are also significant contributors to ADRs.[11] Genetic variations in drug-metabolizing enzymes, drug transporters, and drug targets substantially impact pharmacokinetics and pharmacodynamics.[12] Additionally, genetic factors and structural variations may predispose individuals to certain ADRs.[13] Consequently, a growing number of researchers are focusing on the relationship between genetic factors, inter-individual genetic differences, and genetic variations with ADRs, which has the goal to minimize ADRs caused by genetic variations and achieve optimal therapeutic outcomes.[14]

In recent years, the rapid advancement of pharmacogenomics has enhanced peoples' understanding of ADRs. Pharmacogenomics is the study of variations in human DNA and RNA characteristics related to drug responses, including pharmacokinetics and pharmacodynamics.[15,16] Utilizing information from all genes in the human genome, pharmacogenomics guides the development of new drugs and investigates the influence of genetic factors on therapeutic outcomes at the

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genome-wide level. It is applicable throughout the entire drug lifecycle, including drug target discovery, preclinical research, clinical trials, and post-marketing ADR monitoring.[17] Pharmacogenomics also explores how genetic factors influence individual responses to drug therapies, particularly the associations between genetic variations and ADR risks.[18] Research indicates that pharmacogenomics accounts for over 80% of variability in drug efficacy and safety.[16,19] Approximately 30%–40% of functional variability in 146 clinically relevant pharmacogenes is attributed to rare variants.[20] Over 400 genes are associated with drug efficacy and safety, and more than 240 pharmacogenes are linked to ADRs.[14] Over the past 60 years, pharmacogenomics has been widely applied to identify genetic determinants of drug effects, aiming to maximize drug efficacy while minimizing ADRs.

The article summarizes the genetic basis of ADRs and genes, followed by an overview of the current applications of pharmacogenomics in predicting, diagnosing, preventing, and ensuring the safety of ADRs. It further explores the research status of advanced genomic methods, such as polygenic scoring and multimodal algorithms, as well as international large-scale research projects in the field of ADRs. Finally, the article provides a comprehensive summary of the progress of pharmacogenomics in ADR research, offering valuable insights for future studies in this area.

2. Genetic Basis of Adverse Drug Reactions

Although non-genetic factors, such as age, organ function, inappropriate drug prescriptions, and disease states, can influence drug responses, substantial and growing evidence indicates that genetic variations play a more significant role in altering drug responses and drug clearance.[21] This highlights the genetic basis of many ADRs.

The genetic basis of ADRs lies in individual genetic variations that influence how a person metabolizes, responds to, or tolerates medications.[22]

Studies suggest that ADRs are closely associated with identifiable dysfunctions in the drug epigenetic machinery. The effective processing of any exogenous substance is tightly controlled by a series of enzymes and proteins encoded by specific genes, such as pathogenic genes, mechanistic genes, metabolic genes, transporter genes, and pleiotropic genes, whose regulation and expression depend on epigenetic mechanisms.[22] Specifically, this is reflected in drug-metabolizing enzymes (DMEs), drug transporters, drug signaling pathway proteins, and human leukocyte antigen (HLA). Genetic polymorphisms can impair the activity or function of DMEs, drug transport proteins, and drug targets, significantly altering drug absorption, disposition, metabolism, excretion, and action in patients, ultimately contributing to the occurrence of ADRs.[14] (Shown in Fig. 1).

2.1. Polymorphism of drug-metabolizing enzyme genes

The metabolism of drugs *in vivo* is divided into Phase I and Phase II reactions, mediated by Phase I and Phase II metabolic enzymes, respectively.[23] These enzymes are responsible for eliminating over 95% of clinically used drugs. Sufficient evidence suggests that genetic variations in drug-metabolizing enzymes are associated with interindividual differences in drug exposure and response.[24] For instance, Cytochrome P450 (CYP) is a group of enzymes found in the human body and in the cells of many other organisms that play an important role in drug metabolism and many other biochemical reactions. Variations in genes such as *CYP2D6*, *CYP2C9*, and *CYP2C19* result in differences in enzyme activity, causing some individuals to metabolize drugs either too quickly or too slowly.[25] Individuals with poor metabolic capacity may experience drug toxicity, while ultra-rapid metabolizers may have insufficient drug

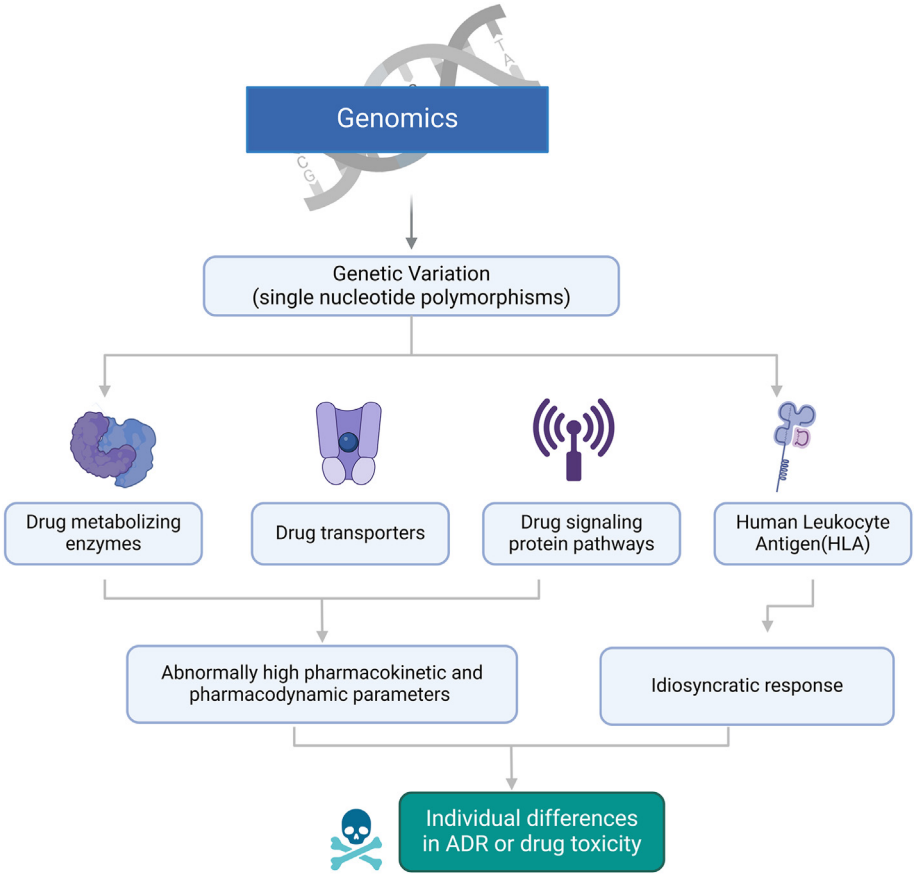

Fig. 1. Genetic basis of adverse drug reactions.

exposure, both of which can lead to ADRs. Therefore, metabolic genes play a significant role in drug transformation, and epigenetic changes in these genes contribute to interindividual differences in drug responses. The polymorphisms of genes encoding the metabolic enzymes can significantly affect enzyme activity, and then influence the metabolic processes of drugs in the body.[26] The relationship between the polymorphisms of certain drug-metabolizing enzyme genes and ADRs is summarized in Table 1.

2.2. Polymorphisms of drug transporter genes

Drug transporters located on the cytoplasmic membrane play a crucial role in the processes of drug absorption, distribution, and excretion.[18] These transporters are primarily categorized into two major classes: uptake transporters, which mediate the entry of drugs into cells, and efflux pumps, which facilitate the secretion of drugs out of cells.[36] Genetic variations in drug transporters can lead to alterations in their activity and protein expression levels, thereby influencing drug responses. Consequently, the genetic polymorphism of transporters is considered one of the key factors determining drug efficacy and the risk of ADRs.[37] Below are several common examples.

P-pg encoded by *ABCB1* is an effervescent transporter widely distributed in renal tubules and tumor tissues, capable of transporting structurally different compounds including cardiovascular drugs, antitumor drugs, and antibacterial drugs. The low expression of P-pg in renal tubular epithelial cells of kidney transplantation donors is closely related to the nephrotoxicity caused by cyclosporine. Sallustio et al. showed[38] that compared with *ABCB1* G1199A subtype, *ABCB1* C3435T subtype reduced the renal clearance of cyclosporine in kidney transplant patients by about 25%, resulting in an increase in blood concentration and further increased the risk of renal toxicity. In another research, the *ABCB1* C3435T subtype led to impaired digoxin transport, elevated serum concentrations, and an increased risk of ADRs.[39] In addition, other variants of *ABCB1*, such as rs1045642, rs2032582, rs1128503, rs2235040, and rs2238476, have also been shown to be associated with ADRs.[40] Organic Anion Transporting Polypeptide 1B1 (OATP1B1) encoded by *SLCO1B1* is an uptake transporter. Mutations in *SLCO1B1* can impair the synthesis of OATP1B1, leading to elevated statin concentrations in the bloodstream and an increased risk of statin-induced myopathy. Studies have confirmed the association of *SLCO1B1* with statin-induced myopathy caused by drugs such as atorvastatin, fluvastatin, lovastatin, and pravastatin.[41]

Table 1
ADRs caused by gene polymorphisms in selected drug-metabolizing enzymes/genes.

Selected drug-metabolizing enzymes/genes	ADRs	References
CYP1A2	1. Caffeine poisoning 2. Side effects of antipsychotic drugs 3. Side effects of antidepressants 4. Toxic reactions of theophylline	27
CYP2C9	1. Bleeding risk associated with warfarin 2. Increased risk of gastrointestinal bleeding caused by NSAIDs 3. Hypoglycemic reactions caused by sulfonylureas	28
CYP2C19	1. Diazepam-induced prolonged sedation neurotoxicity 2. Stent thrombosis and myocardial infarction after clopidogrel administration	29
CYP2D6	1. Arrhythmias caused by antiarrhythmic drugs 2. Opioid dependence 3. Antipsychotic drugs (such as clozapine) increase the risk of extrapyramidal symptoms	30
CYP3A4	Treatment-related leukemia caused by anti-leukemia drugs	31
N-acetyltransferase	1. Sulfonamide-induced allergy 2. Anti-tuberculosis drug-related hepatotoxicity 3. Systemic lupus erythematosus caused by procainamide/hydralazine/isoniazi	32
DPYD	1. 5-Fluorouracil-induced bone marrow suppression 2. Gastrointestinal toxicity 3. Neurotoxicity	33,34
Glucuronyltransferase	1. Irinotecan-induced bone marrow suppression and diarrhea 2. Morphine-induced respiratory depression and excessive sedation	35

NSAIDs: Nonsteroidal Anti-Inflammatory Drugs; DPYD: Dihydropyrimidine Dehydrogenase.

2.3. Polymorphisms of drug target genes

Drug targets significantly influence ADRs, as about 50% of medications achieve their therapeutic effects by binding to receptor targets.[14] Thus, genetic differences in pharmacological targets are essential determinants of therapeutic responses. A substantial number of receptor gene polymorphisms linked to ADRs have been recorded in the PharmGKB database.

The μ-opioid receptor, encoded by *OPRM1*, is a prevalent opioid receptor and the principal target for both endogenous and exogenous opioid analgesics.[42] Research on human μ-opioid receptor gene polymorphism mostly focuses on rs1799971 (118A > G), where its mutation may result in diminished μ-opioid receptor activation and ADRs, including opioid addiction.[43] The polymorphism of the *ADRB2* gene is a crucial factor influencing airway responsiveness to β2-adrenergic agonists. Mutations in the *ADRB2* R16G and *ADRB2* Q27E loci can substantially influence the functionality of ADRB2 receptors, leading to abnormal interactions between β2-adrenergic agonists and ADRB2 receptors. This increases the risk of ADRs.[44]

2.4. Polymorphisms of immune molecule genes

The Human Leukocyte Antigen (HLA) is intricately connected to the operation of the human immune system and serves as a critical pharmacogenomic biomarker related to ADRs. The *HLA* complex is situated on the short arm of chromosome 6 and has more than 100 closely related sites. *HLA* products can be categorized into three classifications based on their distribution, structure, and function. The intricate structure leads to significant genetic variability, linked to ADRs including drug-induced liver injury, Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN), which makes *HLA* polymorphism functions a predictive risk factor for specific ADRs. Moreover, there is growing evidence that many ADRs are associated with an improper immunological response to a medication. This may occur either through direct interaction of the drug with the *HLA* molecule, leading to an inappropriate T-cell response, or through the formation of a covalent bond between the drug and a cellular protein, with *HLA* gene products likely facilitating the presentation of drug-containing peptides from this complex to T-cells.[45]

Amoxicillin-clavulanate was the first drug identified to have an association between *HLA* gene typing and drug-induced liver impairment. This connection pertains to the *HLA-DRB1*1501* allele, which encodes the serum HLA-DR2 protein.[46] Moreover, *HLA-B*57:01* is linked to flucloxacillin-induced hepatotoxicity and hypersensitivity events triggered by nucleoside reverse transcriptase inhibitors, specifically abacavir and nevirapine.[47] Mutations in the *HLA-DRB1*15:01* and *HLA-DQB1*06:02* loci are associated with medication-induced liver injury resulting from the nonsteroidal anti-inflammatory drug Rofecoxib.[48]

Research has demonstrated that T cells participate in drug-induced delayed-type hypersensitivity reactions. Given that HLA genes encode

human leukocyte antigens responsible for presenting antigens to T cells, their genetic variations may correlate with delayed hypersensitivity reactions.[49] Carbamazepine is a principal medication associated with cutaneous hypersensitivity. Research indicated that *HLA-A*31:01* and *HLA-B*15:02* are linked to hypersensitivity reactions and severe cutaneous adverse reactions (SCAR) induced by this antiepileptic medication.[48]

In 2018, the FDA mandated the inclusion of a black-box warning on carbamazepine prescription labels concerning *HLA-B*15:02* and *HLA-A*31:01* genotyping for patients with epilepsy. The advisory suggests genetic testing for people predisposed to HLA mutations prior to carbamazepine therapy. Clinical Pharmacogenetics Implementation Consortium (CPIC) 2016 and Dutch Pharmacogenetics Working Group (DPWG) 2017 guidelines recommend against administering carbamazepine to epilepsy patients who are *HLA-B*15:02*-positive and possess unknown *HLA-A*31:01* genotypes, particularly if they have no prior exposure to carbamazepine. Alternative drugs are advised to decrease the risk of severe hypersensitivity responses, including SJS/TEN.[50]

In addition, there are some newly discovered pharmacogenomic markers that have promising applications but have not been widely validated. Nudix hydrolase 15, encoded by the *NUDT15* gene, is integral to the metabolism of thiopurine medicines, including thiopurine and azathioprine. Research indicates that particular variants in the *NUDT15* gene are significantly associated with thiopurine-induced leukopenia, establishing *NUDT15* as the pharmacogenetic determinant of this condition across many populations.[51] The overexpression of the *FOXM1* gene is associated with the progression of various cancers. The research indicates that *FOXM1* could serve as a potential cancer biomarker in clinical diagnostics.[52] miR-122 is a microRNA predominantly expressed in the liver, significantly influencing liver disease and pharmacological responses. Research indicates that miR-122 serves as a biomarker for liver injury, with alterations in blood levels potentially signaling liver damage earlier than conventional aminotransferase markers.[53] Increasing evidence indicates a significant relationship between ADRs and genetic factors, thereby establishing a foundation for pharmacogenomics in the investigation of these reactions.

3. Application of pharmacogenomics in the research of ADRs

ADRs provide a considerable issue in pharmacotherapy, directly affecting patient safety and therapeutic effectiveness. With advancements in pharmacogenomics, researchers are increasingly recognizing the crucial role of genetic factors in individual drug responses. By analyzing gene polymorphisms related to drug metabolism, drug targets, and immune responses, pharmacogenomics offers new perspectives for predicting, preventing, and personalizing treatment. Progress in this field not only deepens our understanding of the mechanisms underlying ADRs but also brings actionable strategies to clinical practice aimed at reducing drug-related risks and enhancing the precision and safety of treatment. Supported by pharmacogenomics, individualized drug therapy is becoming a reality, driving the broader application of personalized medicine in clinical settings.

3.1. Diagnosis of ADR mechanisms

Traditional pharmacogenomics, mostly derived from randomized controlled trials (RCTS) and meta-analyses, is mostly limited to single drug-gene pairs, and there is no standardization of which genes/variants should be tested to best predict drug response.[54] In addition, the consistency of test results between laboratories is low, so in order to better explore the relationship between drugs and ADRs at the genetic level, cases are often grouped according to the phenotype of patients or the occurrence of ADR, and adverse reactions are defined as the case group and the control group, and the correlation analysis and evaluation are carried out by statistical methods. At present, pharmacogenetic analysis techniques are mainly used in the research, including Candidate gene study, Genome-Wide Association Studies (GWAS), next generation sequencing (NGS) technology and long-read sequencing technology.

3.1.1. Candidate gene study

The study was based on a case-control design in which people using the same drug were selected for prophylaxis. The subjects who developed adverse reactions were carefully described and set as cases, while the control group was subjects who were able to metabolize the same drug normally. Association studies using replication methods to assess the prevalence of genes in certain patient populations may be considered.[55,56] In a retrospective association analysis based on candidate genes,[57] the number of defective alleles (*6, *28, and *60) in the first cycle of ilicotecan monotherapy was found to be significantly correlated with grade 3 or 4 neutrophils by screening, thus determining the association between *UGT1A1* and ilicotecan ADR.

3.1.2. Genome-Wide Association Study (GWAS)

GWAS is an impartial approach for identifying correlations between genotypes and phenotypes in genotyping array or sequencing data. GWAS has been employed to clarify the mechanisms underlying inter-individual variations in medication responsiveness.[58] Genetics influences therapeutic responsiveness, enhancing patient outcomes, mitigating severe adverse events, and decreasing treatment expenses. Furthermore, the release of the UK Biobank and other extensive phenotypic genetic datasets has rendered GWAS a prevalent analytical approach for characterizing numerous phenotypes utilizing genetic data from hundreds of thousands of individuals. Pharmacogenomic investigations of GWAS significantly contribute to understanding the protein networks involved in drug metabolism, transport, and targeting.[59] These networks frequently reveal genetic implications on drug response, which are typically monogenic or oligogenic and exhibit substantial effects. For instance, merely 33 cases were employed to examine the correlation between *NUDT15* and thiopurine-induced leukopenia.[60] Likewise, the initial GWAS of warfarin maintenance dosages comprised merely 181 participants to identify the association between doses and *CYP2C9* and *VKORC1.15*.[61]

GWAS is recognized as highly successful for identifying risk factors linked to specific diseases,[62] while lamoxepine functions as a selective cyclooxygenase-2 inhibitor utilized in the treatment of osteoarthritis and acute pain. Apprehensions over hepatic toxicity have resulted in the retraction or non-authorization of rumiloxib in the majority of significant pharmaceutical markets globally. A case-control GWAS was performed with 41 patients with liver injury and 176 matched patients without liver injury. The *HLA* haplotype *HLA-DRB1*1501-HLA-DQB1*0602-HLA-DRB5*0101-HLA-DQA1*0102* was identified as being related to an increased risk of liver damage caused by lamoxepine ($P = 6.8 \times 10^{-25}$, OR = 5.0).[63] Furthermore, GWAS was employed to assess the impact of clopidogrel on adenosine diphosphate (ADP)-mediated platelet aggregation.[64]

With the continuous development of GWAS research scale, there are more and more large-scale GWAS studies on ADR. The Canadian Pharmacogenomics Network for Drug Safety Consortium performed a GWAS study with 1100 patients and controls matched by vincristine dosage and genetic ancestry.[65] Identifying a statistically significant mutation ($P < 5.0 \times 10^{-8}$) in the *MCM3AP* gene that markedly elevates the risk of neuropathy, along with 12 variants that mitigate neuropathy. These mutations are situated within or next to *SPDYA*, *METTL8*, *PDE4D*, *FBN2*, *ZFAND3*, *NFIB*, *PAPPA*, *LRRTM3*, *NRG3*, *VTI1A*, *ARHGAP5*, and *ACTN1*, offering possible actionable genetic indicators for vincristine neuropathy. It also offers a chance to create tailored interventions to enhance the safety of vincristine administration in pediatric cancer patients.

3.1.3. Next Generation Sequencing (NGS) Technology

The emergence of NGS has transformed the field of genetics, by using targeted sequencing for parallel sequencing of multiple genes, using whole exome sequencing (WES) for exome regions of the genome, or, to a

large extent, using whole genome sequencing (WGS) for entire genomes.[66] These technologies are not only increasingly being used for genetic diagnosis of rare diseases and oncology, but are also beginning to be incorporated into the field of pharmacogenomics. WES and WGS are emerging as key tools for evaluating the association between drugs and ADRs, especially in the areas of precision medicine and pharmacogenomics. WES focuses on the exon region and can effectively detect gene mutations related to drug metabolism and drug targets, especially those that directly affect protein function. For specific drugs or diseases, WES can quickly identify functional mutations and reduce research costs, making it suitable for association studies with large samples.[67]

A WES study was performed on germline DNA from 9 patients with trastuzumab induced cardiotoxicity, and a case-control study was conducted using the Human Gene Mutation Database (HGVD) compared with 1208 general Japanese population. In screening studies, a total of 10 genetic variants were found to be associated with the risk of trastuzumab induced cardiotoxicity (suballele frequency MAF < 0.05 and $P < 0.001$). In a replication study of 10 SNVs in 234 patients, rs139944387 was found to be associated with trastuzumab induced cardiotoxicity.[68] In addition, WES is widely used to mutate CYP450 family genes, which are strongly associated with drug metabolism. However, because WES is unable to capture variation in non-coding regions, associations between important regulatory elements (such as promoters or enhancers) and ADRs may be missed.

In contrast to WES, WGS provides genome-wide coverage, enabling a more comprehensive analysis of drug-related gene and non-coding regulatory variation. The advantage of WGS is that it overcomes the limitations of WES, which is that WGS not only allows better and more accurate sequencing of exome with appropriate coverage, but also sequencing of non-coding regions.[66,69,70] Additionally. the consistent and uniform coverage of WGS facilitates the detection of copy number alterations.[71] Short-read WGS serves as the most extensive short-read sequencing method, providing a foundation for genetic diagnosis and pharmacogenetic evaluation, facilitating the detection of both common and unusual pharmacogenetic variations.[72] WGS has found differences in enhancer and promoter areas associated with drug response regulation, including mutations in the promoter regions of specific drug-metabolizing enzyme genes that may influence gene expression levels and therefore affect drug response. Moreover, whole WGS can identify copy number variants (CNV), insertions, deletions, and other structural abnormalities, thereby elucidating their impact on therapeutic efficacy.[73]

The 100,000 Person Genome Project was launched by the UK government in 2012 and is led by the National Health Service (NHS) and Genomics England. The goal is to advance the development of precision medicine by sequencing the complete genomes of 100,000 participants, providing an important scientific basis for treating rare diseases and cancers. A study of the 100,000 Person Genome Project[74] analyzed the germline WGS of 76,805 participants to identify pharmacogenetic variants in four genes (*DPYD*, *NUDT15*, *TPMT*, and *UGT1A1*) associated with toxicity from five cancer therapeutics (capecitabine, fluorouracil, mercaptopurine, thioguanine, and irinotecan). A phenotypic group-wide association study (PheWAS) was conducted to determine whether phenotypes indicating ADRs were enriched in drug-exposed individuals with associated pharmacogenomics variants. In a subset of 7081 cancer patients, *DPYD* variants were reported to clinicians and results collected. A significant association was found between pharmacogenomics variants in *DPYD* and toxic-related phenotypes in patients treated with capecitabine or fluorouracil.

3.1.4. Long-read sequencing technology

Long-read sequencing is progressively used in pharmacogenomics. The method relies on real-time observation of polymerase activity on an individual template molecule or on optical real-time monitoring of fluorescent nucleotide binding (single-molecule real-time sequencing). The average read length is 20 kb, while the fluctuation of ionic current during the translocation of the nascent DNA strand is measured by nanopore sequencing, which has an average read length of 100 kb.[5] Long-read sequencing has been effectively employed in pharmacogenomics to sequence intricate pharmacogenomic loci.[75,76] In a long-read sequencing study,[77] the *CYP2D6* gene has been sequenced by Pacific Biosciences RSII, yielding high-quality, full-length phasing sequences that provide precise variant identification and haplotype analysis across the whole gene locus, encompassing exons, introns, and adjacent upstream and downstream regions. Moreover, long-read sequencing has been employed to ascertain genetic correlations between pharmaceuticals and ADRs. For instance, current research has established a novel genetic correlation between *HLA-C*07:01* and clozapine-induced myocarditis.[78] Long-read DNA sequencing in tamoxifen-treated patients enhances the genotypic prediction of *CYP2D6*-catalyzed endoxifen production from $R^2 = 0.52$ to $R^2 = 0.79$, hence improving the model for predicting inter-individual variability in tamoxifen responsiveness.[79] In clinical settings, long-read sequencing is not commonly employed due to the absence of established standardized workflows. However, a growing number of successful use cases in clinical diagnosis suggest that a wider range of clinical applications is achievable.[80,81]

3.2. The prediction and reduction of ADRs

Pharmacogenomics can more accurately predict individual drug responses, thereby guiding drug selection and dosage, achieving personalized drug therapy, and avoiding ADRs. In recent years, with the development of pharmacogenomics, Polygenic Risk Score (PRS) and Multimodal Algorithms have been widely used in predicting and reducing ADRs.

3.2.1. Traditional research

Previous research concentrated on the examination of specific genes or gene polymorphisms directly associated with drug metabolism or pharmacological targets, particularly emphasizing functional variations of critical genes to evaluate their impact on drug metabolism or toxicity. The first genotyping test approved by the FDA is the AmpliChip *CYP 450 test*,[82] which used a patient's genetic information to determine the appropriate drug and dosage. The test project can identify many polymorphisms, including the 36 polymorphisms of *CYP2D6* and the two polymorphisms of *CYP2C19* (**2* and **3*). To ascertain their function in the metabolism of amitriptyline, clomipramine, clopidogrel, codeine, desipramine, doxepin, esomeprazole, fluoxetine, imipramine, metoprolol, nortriptyline, omeprazole, and other pharmaceuticals. Recent approvals of additional pharmacogenomic tests aim to reduce ADRs stemming from human genetic variations and to prevent patients from obtaining inadequate dosages of unsuitable treatments.

In addition, additional studies have identified high-risk genes that may cause ADR through randomized controlled clinical trials and various methodologies, and adjusted rational drug use to avoid or alleviate ADR as effectively as possible. In a 6-week randomized controlled clinical trial named PREDICT-1,[83] data analysis revealed that over 50% of patients who tested positive for *HLA-B*5701* acquired immunologically proven hypersensitivity, but none of the patients who tested negative for *HLA-B*5701* exhibited hypersensitivity. The findings of this clinical trial were noteworthy, as premedication genetic screening markedly decreased the occurrence of abacavir hypersensitivity, ultimately resulting in the incorporation of *HLA-B*5701* allele screening recommendations prior to medication in clinical guidelines and approved product descriptions for abacavir.

Clopidogrel, an antagonist of platelet adenosine diphosphate (ADP) receptors, is used to reduce atherosclerotic thrombotic events in patients with a recent history of myocardial infarction, stroke, peripheral arterial disease, and acute coronary syndrome. Clopidogrel is a precursor with no antiplatelet activity, but 15% of the dose *in vivo* is metabolized to active metabolites through a 2-step process involving multiple CYP enzymes, one of which is the polymorphic *CYP2C19*. In a clinical trial called

TRITON-TIMI38,[84] carriers of the LOF *CYP2C19* allele had higher rates of death and non-fatal heart attacks compared with non-carriers. Based on the results of these multiple clinical studies, the label of clopidogrel has been modified several times to include pharmacogenomic information associated with reduced antiplatelet response and increased risk of cardiovascular events in patients with reduced *CYP2C19* function.[85]

3.2.2. Polygenic risk scores

In polygenic diseases, individual variations are insufficient for evaluating disease risk. The genetic load resulting from a combination of risk variants is essential for obtaining a sufficiently informative measure to identify individuals at high risk. Genetic risk is typically evaluated using PRS, which represents the weighted sum of the risk alleles possessed by an individual.[86] PRS is typically produced from GWAS. With an increase in cohort size, PRS for prevalent diseases can detect a greater number of at-risk individuals compared to infrequent single-gene mutations, which include 7 million individual variants such as coronary artery disease, atrial fibrillation, diabetes mellitus type 2, and inflammatory bowel disease.[87]

The PRS is a comprehensive tool that combines the effects of many different genetic variants into a single indicator, allowing one to predict a given phenotype and infer genetic overlap between traits. As a result, they can provide information throughout the life course, from perinatal risk prediction to diagnostic support, to guide treatment decisions, and prognosis of disease processes and outcomes.[88]

At present, many clinical applications of polygenic risk scores focus on cardiovascular disease, type 2 diabetes, breast cancer, and Alzheimer's disease. Khera et al.[87] demonstrates in the UK Biobank that PRS can identify which percentage of samples have at least a three-fold increased risk of coronary artery disease, atrial fibrillation, diabetes mellitus type 2, inflammatory bowel disease, and breast cancer. In pharmacogenomics, the majority of PRS research concentrates on optimizing anticoagulant dosage.

The risk of major adverse cardiovascular events associated with clopidogrel was linked to a PRS comprising six genetic variations. However, no individual variants demonstrated a meaningful correlation with cardiovascular mortality after adjusting for *CYP2C19*2*.[89] Moreover, PRS investigations involving eight pharmacogenomic variations, including *CYP1A*, *UGT1A*, *UGT2B*, *CYP2C*, and *POR* loci, demonstrated an explanation of 7.3% of the variance in clozapine metabolic rate.[90] A comprehensive study[91] involving over 560,000 individuals from Finland, the Estonian Biobank, and the UK Biobank demonstrated the impact of genetics on drug use patterns, highlighting significant polygenicity within the genetic architecture, which included 40 loci not associated with potential therapeutic targets, suitable for the generation of PRS. To forecast and avert cardiometabolic disorders.

There were significant differences in the number of variations between PRS of drug response and disease risk score. PRS for pharmacogenomics typically includes fewer than 10 variants, while PRS for common diseases can cover millions of variants,[92] suggesting that extending PRS to include more pharmacogenomics-related variants could significantly enhance its predictive performance. For clinical applications, the integration of PRS into the electronic health record (EHR) can help doctors to fully understand the genetic background of patients before prescribing, so as to select safer drugs and dosages, to a certain extent, reduce the occurrence of ADRs.[93]

3.2.3. Multi-modal algorithms

Multi-modal algorithms combine multiple data sources (genomic data, phenotypic data, electronic health records, and environmental factors) to analyze complex drug response patterns using machine learning and artificial intelligence techniques.[94] Compared with single data analysis, multi-model algorithms can capture more dimensional information and improve prediction accuracy. In terms of data integration, by integrating patients' multi-dimensional data such as genome, epigenetic, transcriptome, and environmental factors, the complex mechanism of ADR can be effectively analyzed, genetic susceptibility can be identified, and personalized risk prediction models can be built. Patients' genetic data were combined with clinical history, medication records, and biomarkers (such as liver and kidney function indicators) to comprehensively assess ADR risk.

Web-based approaches have been developed to integrate multiple data sources such as drug-target interactions (DTI), drug-drug interactions (DDI), and protein-protein interactions into one drug-target prediction framework. In these networks, the nodes can be drugs or proteins, and the edges are indicators of interactions or similarities between the connecting nodes.[95] In this way, omics data (also known as heterogeneous data), such as ADRs, drug-disease associations, and genomics data, have been used to enhance DTI predictions. For example, Luo et al.'s[96] proposed DTINet learns low-dimensional feature representations of drugs and target proteins from heterogeneous data and uses induction matrix completion to predict DTI. Wan et al.[97] developed an end-to-end approach called NeoDTI, which can integrate various information from heterogeneous network data and automatically learn topological retention representations of drugs and targets to further facilitate DTI predictions.

In addition, there is some research using emerging computer-aided tools combined with pharmacogenomics, using multi-model algorithms to predict ADRs. A study developed a machine learning model to forecast ADRs and assess drug safety throughout early development, achieving an overall prediction accuracy of 82%. Furthermore, the reverse docking program INVDOCK was used to study adverse reaction associated proteins to predict associated adverse reactions, with an accuracy of more than 60%.[98] In addition, they adopted an advanced data mining method to predict potential ADRs by establishing gene-adverse reaction relationship network. The results also proved that this gene-adverse reaction relationship network can not only be used as an effective tool for drug safety assessment, but also predict potential ADRs at the gene level, which is helpful to understand the mechanism of ADRs.[99] Another study used Google's PageRank algorithm to build a database of serious adverse reaction-gene relationships, and used clozapine induced granulocytic deficiency as an example to study drug off-target, off-system, and off-target interactions through compound-protein interactions.[100] To provide a theoretical basis for understanding population-specific serious adverse reactions.

3.3. Improvement of drug safety monitoring

3.3.1. Traditional ADR monitoring methods

ADRs and safety studies are important research content of drug safety supervision, encompassing the entire drug development process, beginning with the research design phase.[101] Traditional ADR monitoring methods mainly include spontaneous reporting system (SRS), intensive hospital monitoring (IHM), and prescription event monitoring (PEM).[102] Table 2 presents common, prevalent, and conventional ADR monitoring techniques. Despite active analytical surveillance, the design of modern ADR surveillance studies has some limitations: ADR monitoring mainly relies on voluntary reporting. Underreporting, misreporting, and missing ADR events caused by evaluator subjective bias, as well as imperfect ADR event information, will greatly reduce the sensitivity and accuracy of ADR monitoring, and it is often difficult to timely detect rare and special adverse event signals due to time lag.[103] In addition, patients were not subdivided into high-risk and low-risk groups because some of the reported drug outcomes may be specific to certain subpopulations, while causal relationships between drugs and events cannot be determined because they do not assess the underlying mechanisms of ADR. Therefore, traditional ADR monitoring studies require modern methodologies to proactively avert ADRs, classify patients into risk categories, and elucidate the mechanisms of medication toxicity and ADRs.[104]

3.3.2. The application of pharmacogenomics in pharmacovigilance

Pharmacovigilance studies can monitor drug-associated adverse

Table 2
Surveillance methods for ADRs and methods of proving associations.

Method	Advantages	Disadvantages
Anecdotal reporting	1. Simple 2. Cheap	1. Relies on individual vigilance and astuteness 2. Relatively common effects detected only
Voluntary organized reporting	Simple	Under-reporting
Intensive event monitoring	Easily organized	Selected population studied for a short time
Cohort studies	1. Prospective 2. Good at detecting effects	1. Large numbers required 2. Expensive
Case-control studies	Excellent for validation and assessment	1. New effects not suitable 2. Expensive
Case-cohort studies	Rare effects suitable	Complex calculations
Population statistics	Large numbers can be studied	1. Difficult to coordinate 2. Poor quality of information
Record linkage	Excellent if comprehensive	1. Time-consuming 2. Expensive 3. Retrospective
Meta-analysis	Uses data that have already been obtained	Need to obtain unpublished data; Heterogeneity of different studies

events, which are incidents that occur during a patient's usage of a medication, regardless of their direct correlation to the medicine. Adverse Drug Events (ADE) encompass all drug-related negative occurrences, including medication errors, overdoses, drug interactions, and further complications. Pharmacogenomics can bridge the gap in conventional pharmacovigilance research by elucidating the potential relationship between drug exposure and the manifestation of ADRs. Pharmacovigilance can thus assess the variability of population responses to medications, while pharmacogenomics elucidates this variability. Currently, several research indicate that pharmacovigilance and pharmacogenomics converge to create Pharmacogenovigilance (PgV), which offers insights and direction for pharmacovigilance efforts via pharmacogenomic analysis.[105] It can identify subgroups at heightened risk for ADRs, thereby facilitating targeted drug development, marketing, and oversight. Additionally, population-level extrapolation of monitoring signal results can also be performed, while pharmacovigilance can also fill in pharmacogenomics studies.[106]

Current pharmacogenetic vigilance procedures can be divided into two categories: those that perform genotyping prior to signal detection and those that perform targeted genotyping based on signal detection.

Genotyping prior to signal detection involves examination of candidate genes or high-throughput genotyping to facilitate the eventual linkage of this genetic data with treatment-relevant signals produced during a patient's clinical management. Clinically actionable pharmacogenomics results will be integrated into the patient's EMR to inform treatment decisions. A study by the University of Florida Institute for Clinical and Translational Science[107] created a pharmacogenomic alert in clopidogrel's EMR with adequate sample and information processing, and evaluated the alert's effectiveness, prescribing changes, and impact on drug efficacy and safety.

Targeted genotyping after signal detection involves selecting patients with ADE for genotyping. This approach was adopted by the Pharmacovigilance Center in the Netherlands to study the feasibility of informing pharmacists or physicians that pharmacogenomics may be involved in the pathogenesis of ADR, thereby further identifying the potential role of genotyping. The nested case-control study design developed in the New Zealand Intensive Drug Surveillance Programme (NZIMMP) similarly applies this approach, linking prescription event monitoring studies to pharmacogenomics: nearly complete records of all patients who have access to a widely used class A new drug over the entire surveillance period (4–5 years). Patients who developed mental or visual impairment after using COX-2 inhibitors were selected from the IMMP monitoring database and matched with controls. In addition, the PREDICT project, the Canadian Pharmacogenomics Network for Drug Safety (CPNDS), and the International Serious Adverse Event Consortium (iSAEC) have been conducting genomic analyses of selected patients with severe ADRs versus matched control patients.

Targeted genotyping after signal detection entails the selection of patients with ADE for genotyping. The Pharmacovigilance Center in the Netherlands implemented this strategy to assess the feasibility of notifying pharmacists or physicians that pharmacogenomics may contribute to the pathophysiology of ADR, hence elucidating the possible significance of genotyping. The nested case-control study design established by the New Zealand Intensive Drug Surveillance Programme employed a similar methodology, connecting prescription event monitoring studies to pharmacogenomics. By utilizing nearly comprehensive records of all patients with access to a widely utilized class A new drug throughout the entire surveillance duration. Patients who experienced mental or visual impairment following the use of COX-2 inhibitors were extracted from the IMMP monitoring database and paired with control subjects.[108] Furthermore, the PREDICT project,[109] the Canadian Pharmacogenomics Network for Drug Safety,[110] and the International Serious Adverse Event Consortium (iSAEC)[111] have been performing genomic analysis on specific patients experiencing severe ADRs compared to matched control patients.

European Medicines Agency (EMA) has formulated a concept paper outlining seven essential elements for establishing recommendations that utilize the pharmacogenomics technique in pharmacovigilance.[106] Two of them are: "early consideration of when monitoring or collection of post-authorization genomic data may be required to confirm appropriate dosing and combination administration, as well as to provide information or recommendations based on identified genomic biomarkers" and "collection and storage of genomic material (e.g., DNA or otherwise) during clinical trials and in the event of severe ADR under conditions of lack of efficacy post-authorization or accidental deterioration". Therefore, pharmacovigilance should be further developed, prospectively and proactively performed for pharmacogenomics analysis. Conduct a genome-wide scan in advance or identify pathway genes associated with drug elimination and mechanisms of action, and correlate them with ADRs. Following the assessment of various research, the genetic test outcomes will be converted into treatment protocols that may adjust the regimen or dosage for patients with high-risk genetic polymorphisms to ADRs and ADEs.

3.4. Development of personalized medicine and precision medicine

The goal of modern medicine is to provide individuals with the best treatment in terms of efficacy and toxicity, based on genetic and molecular data.[61] As a result, personalized medicine and precision medicine are increasingly used, with the goal of classifying patients into personalized treatment categories using a data-driven approach. Pharmacogenomics represents an integral part of personalized medicine and precision medicine,[112] where the goal is to tailor procedures and treatments to an individual's composition (disease subtype, genetic, environmental, and clinical) to maximize success and minimize any potential adverse effects. From a pharmacogenomics perspective, it is driven in part by research aimed at elucidating the relationship between genes, phenotypes, and risk outcomes. By quantifying the impact of genomic variants on risk outcomes, models can be developed to predict complex risks and guide individual treatment decisions. As the statistical ability to detect molecular and genetic markers of human disease increases, personalized therapy will increasingly be used in patient care.[113]

In terms of ADR research, given the heterogeneity of the world's populations, providing personalized treatment is critical to preventing ADR. By knowing a patient's genetic information, doctors can choose the most appropriate drug and dose based on the patient's genetic profile, thus providing a personalized treatment plan. For people with a high risk

of ADR genotype, personalized and effective alternative therapies can be carried out, such as the selection of appropriate drugs, the calculation of drug dosage, and the avoidance of ADR based on genetic and environmental factors, so as to improve the treatment effect and reduce the disease burden.

A number of medical centers have implemented pharmacogenetic testing into practice to help guide drug therapy.[114] To facilitate implementation, the Clinical Pharmacogenetics Implementation Consortium (CPIC) and Dutch Pharmacogenomics Working Group (DPWG) provide genotype-based prescribing recommendations, which address approximately 20 genes and over 100 drugs to date, including very commonly used drugs, e.g., antidepressants, opioids, antiplatelets/anticoagulants, proton pump inhibitors, and statins.[10,115] The FDA promotes genetic testing before initiating certain medications.[116]

In addition, some studies have analyzed the outcomes of pharmacogenomics in relation to rational medication use, revealing that pharmacogenomics can promote personalized medicine and precision medicine, thereby reducing the occurrence of ADR. Swen et al. elucidate the effectiveness of pharmacogenomic testing utilizing gene combinations to avert ADRs in an open-label, multicenter, controlled, cluster-randomized, cross-implemented trial involving 6944 patients across 7 countries.[117] The test was conducted on patients selected from 7 nations and various settings. Genotype-guided therapy utilizing pharmacogenetics markedly decreases the occurrence of clinically significant adverse medication responses and can be integrated into various European healthcare system structures and settings. The extensive implementation can enhance the safety of pharmacotherapy.

4. International pharmacogenomics consortia and networks efforts

With the continuous development of pharmacogenomics, more and more countries, regions, and organizations began to join in the research of pharmacogenomics, established and constructed a series of representative research institutions, carried out a series of international cooperation and large-scale studies, and effectively promoted the application of pharmacogenomics in ADR research. In particular, the focus on data sharing, technical standardization, and multi-center collaboration has effectively promoted the development of global pharmacogenomics, providing important support for identifying the genetic mechanism of ADR, optimizing personalized therapy, and improving drug safety.

4.1. PharmGKB

The Pharmacogenetics and Pharmacogenomics Knowledge Base (PharmGKB) is presently the most authoritative and comprehensive pharmacogenomic resource. Developed by the National Institutes of Health (NIH), PharmGKB serves as a primary repository of pharmacogenomic data, detailing the impact of human genetic variation on drug response. Comprises medication dosing guidelines, drug label annotations, clinical and variation comments, drug-centered pathways, drug-gene summaries, and the interrelation of genes, drugs, and diseases. PharmGKB consolidates, oversees, and combines premier pharmacogenomic data sets to create a database of genetic variations affecting drug response.[118]

PharmGKB has four main levels of clinical evidence.

A. 1A indicates that there is a large amount of clinical data support, and clinical guidelines or FDA explain specific mutant alleles in detail, focusing on the analysis of the impact of single nucleotide mutations on the genotype and its phenotype, which meets the highest standards for clinical application.
B. 1B indicates that there is high-quality evidence, but the clinical guidelines or FDA did not explain the specific mutation allele, and the evidence level is lower than 1A.
C. 2A and 2B are medium levels of evidence. 2B indicates that there is moderate evidence in multiple repetitive studies, but some of them are not statistically significant or have small effect sizes. 2A indicates that on the basis of meeting 2B, it must be defined as a very important drug gene in PharmGKB, and this gene may have functional significance.
D. 3 is low evidence levels that is, it's significant in a single study (no reproducibility), or there have been multiple studies, but there is no obvious evidence of correlation (no significant difference).
E. 4 is level of opposing evidence, indicating that the existing evidence does not support the relevance of gene drug therapy, and further verification is needed.

4.2. Clinical Pharmacogenetics Implementation Consortium (CPIC)

The Clinical Pharmacogenetics Implementation Consortium (CPIC) was founded in 2009 by the NIH and PharmGKB. CPIC aims to offer pharmacogenomics support tailored to clinical and laboratory needs.[119] Besides providing PharmGKB recommendation grades and FDA labeling, CPIC has evaluated over 400 gene-drug pairings and released recommendations in 24 published guidelines for 106 gene-drug pairs with adequate evidence for at least one prescribing behavior.[10] The CPIC guidelines are formulated in a uniform way. The CPIC employs a standardized system for evaluating evidence that associates genes with phenotypes, categorized into three levels: high, medium, and weak. They employ a system with three tiers of suggestions: strong recommendations, medium recommendations, and optional recommendations. Robust and unpretentious guidelines are being formulated and disseminated for various categories of gene-drug combos. "Strongly recommended" indicates that the evidence quality is high and the anticipated effect is markedly superior to the expected effect, whereas a "moderate" recommendation signifies an ambiguous or close balance regarding the quality of the evidence and the anticipated effect being significantly greater than the expected effect.[120]

CPIC employs an investigative methodology to assess drug-gene combinations, then refined by a multidisciplinary writing committee that appraises the evidence and formulates clinical recommendations. The overarching guidelines encompass background information, a review of pertinent literature, the scope of issues, risks associated with clinical decision-making, drug-drug interactions, nomenclature, identifiable genes, gene-based dosing recommendations, potential risks and benefits, warnings, and the state of implementation, among other topics. It encompasses mutation site data, pharmacokinetic and pharmacodynamic effects, and integrates high-quality clinical trial outcomes premarketing and post-marketing to formulate clinical practice recommendations, including dosage determination and gene detection initiatives.

4.3. The Dutch Pharmacogenetics Working Group (DPWG)

The Dutch Pharmacogenetics Working Group (DPWG) is a multidisciplinary working group funded and established by the Royal Netherlands Pharmacists Association in 2005 with the goal of making clinical dosing recommendations based on pharmacogenomics. And input the information into the digital monitoring system.

DPWG has been formulating guidelines for over a decade that advocate for the prescription and dispensation of medications tailored to patients with specific genotypes necessitating intervention, particularly those at elevated risk of ADRs, thereby recommending dosage adjustments.[121] Thus far, the DPWG has evaluated over 100 gene-drug pairings. The DPWG identifies 60 gene-drug combinations as gene-drug interactions necessitating interventions such as dose modification or monitoring for adverse effects. The remaining gene-drug pairings necessitate no further action or monitoring for pharmacogenetics. 18 gene-drug combinations are categorized as gene-drug interactions that necessitate no action; 29 gene-drug couples are classified as non-interacting and also require no action.[122]

The DPWG categorizes the levels of evidence into five ascending tiers, from 0 to 4, with level 4 requiring the presence of rigorously controlled trials that yield pertinent pharmacokinetic or clinical endpoint outcomes. The suggested strength is categorized into seven grades, ranging from low to high: AA, A, B, C, D, E, and F.[123] Each guide or scientific publication assigns two scores to every combination of genotype or projected phenotype and a certain medicine. The cumulative score for each combination represents the highest degree of evidence and the greatest relevance across all articles in the evaluation. Initial dose modifications are determined using pharmacokinetic data for patients with a particular genotype or anticipated phenotype. Recently, the DPWG formulates the Clinical Implementation Score to instruct and assist healthcare providers in performing pharmacogenetic testing before or during therapy with a particular medication. The evaluation criteria encompass clinical efficacy, evidence level, extent of genotyping necessary, and pharmacogenetic data. The overall score corresponds to three tiers of pharmacogenetic testing in clinical practice: potentially advantageous, beneficial, and required.[124]

4.4. Canadian Pharmacogenomics Network for Drug Safety

The Canadian Pharmacogenomics Network for Drug Safety (CPNDS) initially focused on exploring genotype-specific therapies for pediatric patients, and later focused specifically on drug safety issues caused by genetic polymorphisms. It is committed to predicting serious adverse drug reactions before administration and has established a unique active adverse reaction monitoring network.[125]

When CPNDS formulates the pertinent pharmacogenomically-guided medication guidelines, the guideline development committee is interdisciplinary and includes patients and healthcare policymakers. The formulation of the guidelines includes:[126] (1) A systematic literature review; (2) An analytical assessment of the acquired evidence; (3) Formulate clinical practice recommendations during a seminar with guideline development group members; (4) Members of the guideline development team perform an internal review of the draft guideline; (5) External evaluation by subject matter experts and representatives of the target audience.

The GPNDS guidelines comprise five clinical recommendations: cisplatin and auditory impairment, anthracycline and cardiotoxicity, warfarin and hemorrhage, carbamazepine and hypersensitivity, and codeine.[119] GPNDS has two grading systems: the overall evidence score system and the clinical practice recommendation system. The evidence rating system comprises four levels (+ to ++++), where a low rating of + signifies that "conclusions cannot be drawn or may be altered by future research, and the existing evidence is unpromising", while the highest rating, ++++, denotes that "robust general conclusions can be established that are unlikely to be modified by subsequent research". Clinical practice guidelines are categorized into three grades: "A: Strong, B: Moderate, and C: Optional." An A ranking signifies conclusions grounded in robust scientific evidence, where the advantages distinctly surpass the risks, while a C rating indicates predominantly reliant on expert opinion for the advancement of evidence within a research framework. Middle-grade recommendations necessitate tailored, informed decision-making by patients and healthcare providers.[110]

4.5. Pharmacogenomics consortia and networks

The advancement and application of pharmacogenomics in ADRs necessitate substantial sample numbers, passively gathered longitudinal data, and genomic datasets from varied populations. In most prior studies assessing efficacy and detecting toxicity or pharmacogenomic interactions, participant samples were generally linked to a restricted scope of phenotypic information. Furthermore, access to the foundational data is frequently restricted to researchers, organizations, or commercial entities directly engaged in the study, hence constraining the advancement of pharmacogenomics in ADR investigations. Consequently, many nations have progressively formed national or regional large genomics consortia or networks to enhance the efficiency of extensive genomic and non-genomic analyses, centralize specimen collection, streamline sample processing, passively integrate longitudinal health information from EHRs, and disseminate data. The biobank was intentionally conceived as a comprehensive longitudinal cohort study to facilitate continuous support for ADR research. Access to numerous biobanks facilitates rapid and extensive discovery and replication analyses, with results being broadly disseminated. In contrast to extensive cohorts with limited sample sizes, centralized biobanks can streamline and methodically handle samples and data to expedite large-scale genomic analyses.[113]

The overview of large-scale and commonly used international pharmacogenomic information databases and networks is shown in Table 3.

5. Conclusions

ADRs are a major problem in drug therapy, which brings a huge economic burden to individuals and society. Genetic variants are a contributing factor to clinical ADRs, and there is growing evidence of an association between genetic variants and identified ADRs, some of which have been recognized by FDA and PharmGKB. Pharmacogenetic mechanism is the integration of pathogenic genes, target genes, metabolic genes, transport genes, and immune molecular genes, and the polymorphism of these genes leads to the occurrence of ADR. At present, pharmacogenomics has played an important role in explaining ADR, predicting and reducing ADR, optimizing drug dosage, promoting drug reevaluation and label updating, personalized medicine, and strengthening drug safety supervision, and has shown unique value. In addition, the large-scale research carried out by more and more countries and regions and the establishment of large-scale pharmacogenomics networks also provide a strong boost to its development. In the future, pharmacogenomics of ADR research still has broad prospects.

Pharmacogenomics has ushered in unprecedented development opportunities in China, thanks to the continuous promotion of precision medicine policies, the accumulation of large-scale population genetic data, the growth of clinical precision medicine demand, and the rapid progress of genetic testing technology. In the "Healthy China 2030" plan, the government emphasizes the development of precision medicine, and improves the regulatory system related to pharmacogenomics to provide policy support for personalized medicine. At the same time, China's large and diverse population genetic background provides rich data resources for pharmacogenomics research, and combined with the improvement of

Table 3
Influential pharmacogenomic Consortia and Networks.

Consortia and Networks	Country	Region	Number of Enrolled Participants
All of Us	United States	North America	823,000
BioVU	United States	North America	300,000
Kaiser Permanente Research Bank	United States	North America	400,000
Mass General Biobank	United States	North America	145,000
Michigan Genomics Initiative	United States	North America	100,000
Million Veteran Project	United States	North America	1,000,000
Biobank Japan	Japan	Asia	260,000
China Kadoorie Biobank	China	Asia	512,000
Estonian Biobank	Estonia	Europe	200,000
FinnGen	Finland	Europe	556,000
Genes & Health	United Kingdom	Europe	62,159
Our Future Health	United Kingdom	Europe	1,722,329
UK Biobank	United Kingdom	Europe	502,000

local gene databases, it is helpful to develop personalized drug use schemes that are more in line with the characteristics of the Chinese population. In addition, the growing demand for precision medicine in the fields of tumor targeted therapy and cardiovascular disease management has promoted the transformation and application of pharmacogenomics in clinical practice, while advances in gene sequencing and artificial intelligence technology have further reduced the cost of detection, improved the accuracy of genomic data interpretation, and helped the wide application and development of pharmacogenomics in China. In China, with the tide of precision medicine, the optimization of more sequencing methods and the drive of real-world data, the scope and depth of research can be expanded in the future. By improving the diversity of pharmacogenomic data and updating and perfecting large-scale pharmacogenomic networks, multiple subjects such as regulatory agencies, pharmaceutical industry, medical community and drug users can be included. To realize the effective docking of scientific research and practical application, and actively promote the application of pharmacogenomics in the clinical practice of ADR research, so as to provide a solid foundation for the safe drug use of the people.

CRediT authorship contribution statement

Hongyu Bi: Writing – original draft, Methodology. **Jun Zhu:** Writing – original draft. **Yuanxuan Cai:** Visualization, Software. **Xiaofang Shangguan:** Data curation. **Zherui Chen:** Data curation. **Maimoon Shihab Ahmed:** Validation. **Rui Huang:** Writing – review & editing, Supervision, Investigation, Funding acquisition, Conceptualization.

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Declaration of competing interest

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