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Database issue

PersADE: a database of personalized adverse drug events and their underlying molecular mechanisms

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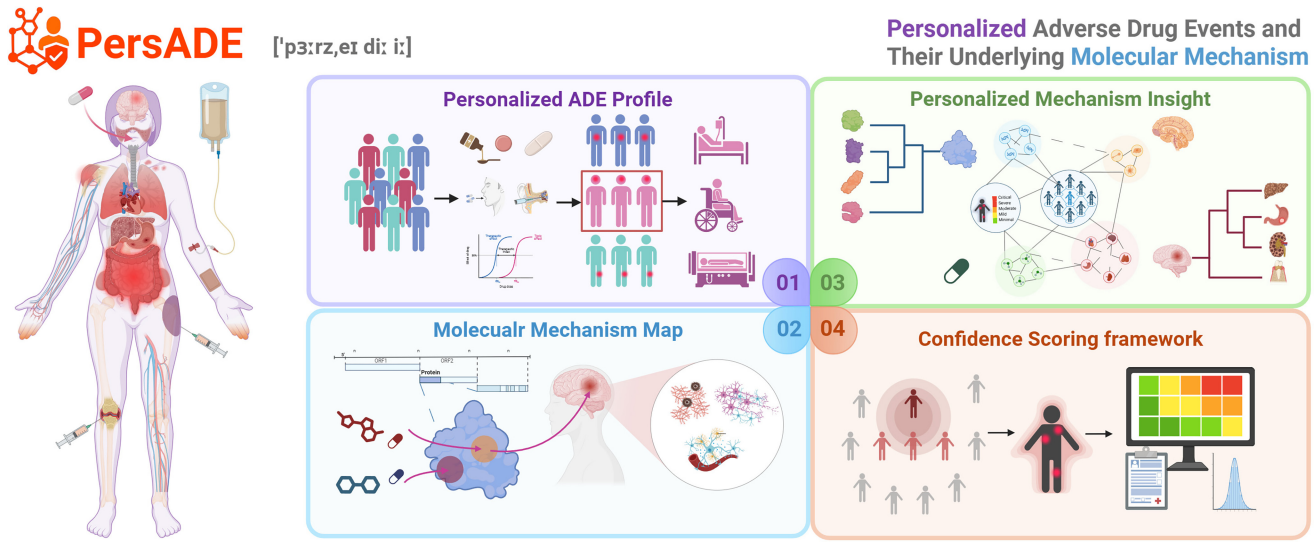
Abstract

As a major burden on global healthcare systems, adverse drug events (ADEs) result in significant morbidity, mortality, and healthcare resource consumption. With the rapid advances in precision medicine, personalized ADEs and their molecular mechanisms are important components of drug repurposing and drug safety improvement. Thus, extensive studies have been conducted to collect valuable information on personalized ADEs, but no database has yet been available to provide such data. In this work, PersADE, a database aiming to provide personalized drug adverse events and their molecular mechanisms, was constructed. It integrated 4 061 772 personalized drug-ADE associations, 31 756 protein-ADE associations, and 108 677 drug-protein interactions, with a particular emphasis on off-target effects. The uniqueness of these data lies in (a) providing demographic characteristics, disease context and drug administration parameters associated with ADEs, enabling stratification of drug-ADE associations; (b) systematically integrating interactions among drugs, human proteins and ADEs, describing the mechanistic insights. Given the growing global focus on precision medicine, PersADE is highly anticipated to significantly impact studies on personalized ADEs and mechanistic explorations by providing researchers and clinicians with evidence-based tools. It is now freely accessible at: https://idrblab.org/PersADE

Graphical abstract



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Introduction

As a critical burden on global healthcare systems, adverse drug events (ADEs) account for about 110 000 deaths, 5 billion dollars in direct medical expenditures, and 5.0% of emergency hospital admissions annually [1–3]. To deal with these burdens, recent research reported that personalized ADEs and the underlying molecular mechanisms (the association between drugs and personalized ADEs; the association between drug and human proteins, especially off-target; and the association between human protein and personalized ADEs) can offer valuable insights [4–6], which has been adopted in the identification of novel therapeutic targets for various diseases [7, 8], the successful drug repurposing exemplified by sildenafil from angina treatment to erectile dysfunction therapy [9, 10], the precision dosing of critical medication such as warfarin and digoxin for safety profile enhancement [11–13]. Pharmacogenomic data from resources such as PharmGKB [14] have demonstrated that genetic variants significantly influence drug response and ADE susceptibility. In other words, there is an urgent demand to collect such data to overcome the ADE-related challenges and assist in the progression of precision medicine.

Until now, a variety of resources have been constructed for ADE-related research, which can be grouped into four classes. (a) *ADE term-centered resources* describe systematic characterizations and a mechanistic context for adverse events. Examples include ADReCS [15] offering a hierarchical ADEs classification system, and ADReCS-Target [16] mapping the adverse events to molecular targets and biological genes. (b) *drug-centeredresources* focus on the description of drugs and integrating comprehensive information, such as DrugBank [17], DrugCentral [18] and DrugMAP [19]. (c) *target-centered resources* focus on biological targets and their associations with disease, including ChEMBL [20], UniProt [21], and Open Target [22]. (d) *drug-ADEassociation-focusedresources* concentrate on the relations between drugs and adverse events. These include regulatory reporting systems such as the *FDA Adverse Event Reporting System* (FAERS), VigiBase, and EudraVigilance, which capture real-world drug safety signals; the curated database SIDER [23] standardizing label-derived drugs-ADEs associations; CTD [24] exploring causal relation among toxicologic pathways, chemical exposure and disease; and OFFSIDES [25] employing statistical inferences to derive high-quality drug–ADE pairs. These resources have been widely used by academia, industry and regulators. As reported, personalized ADEs and their underlying molecular mechanisms are of particular importance [6, 26, 27], but the existing databases have not specifically focused on this aspect. In other words, it remains highly demanded to have a knowledge base that can systematically describe such important data.

Therefore, we constructed PersADE, a database systematically integrating patient-level contexts, ADE annotations, therapeutic properties and associated human proteins to elucidate the underlying molecular mechanisms. PersADE is unique in three aspects. First, comprehensive molecular mechanism mapping. It included a total of 4 061 772 associations between drugs and ADEs, 31 756 associations between proteins and ADEs, and 108 677 associations between drugs and proteins (especially, the off-targets). 6980 ADE-associated proteins belonging to key protein classes (enzyme, GPCR, ion channel, nuclear receptor, transporter, *etc.*) are collected, which are linked to 348 KEGG [28] and 6191 MSigDB [29] pathways. Second, personalized ADE mechanism insight. Based on the above associations and over 115 000 peer-reviewed references, PersADE implemented a robust association confidence level system to assess molecular mechanisms underlying adverse events, which helps measure millions of personalized and general drug-ADE associations spanning over 10 000 compounds and 19 000 ADE terms. Furthermore, it also integrated report frequency, event ratios, and statistical significance into a unified personalized scoring framework to evaluate the reliability of 3 908 596 personalized associations and 1 804 084 general associations derived from 11.5 million patient-specific case reports. The above data provided a systematic insight for elucidating personalized ADEs at the molecular level. Third, a multi-parameter visualization function. All in all, PersADE enabled sophisticated queries across ADE nomenclature, chemical structures, therapeutic categories, human proteins, patient characteristics, and clinical contexts, which could be freely accessible by all users without login requirement at: https://idrblab.org/PersADE.

Factual content and data retrieval

Data collection for personalized ADEs and their underlying molecular mechanisms

PersADE implemented a hierarchical three-tier architecture that incorporates heterogeneous data sources, enabling the comprehensive characterization of personalized ADEs and the mechanistic exploration of the molecular underpinning (as shown in Fig. 1). This database integrated over 11.5 million spontaneous reports from FAERS and *Canada Vigilance Program*. Through rigorous data cleaning and processing using standardized protocols, patient demographic characteristics, clinical outcomes and medication parameters were extracted, ultimately yielding 4 061 772 personalized drugs-ADEs associations. These associations contain critical individual factors (such as age, sex and diseases), supplemented by 2 201 568 drug-ADE associations partially from CTD [24], SIDER [30], and OFFSIDES [31], thereby providing a comprehensive data foundation for personalized risk assessment.

To elucidate the molecular mechanisms underlying ADEs, our database constructs multi-layer molecular interaction networks. It incorporates 31 756 ADE–protein associations from ADReCS-Target [16] and CTD [24], together with 108 677 drug–protein interactions from multiple sources. Among these, 17 208 drug–protein interactions with experimentally validated quantitative binding affinity data were specifically obtained from ChEMBL [20], BindingDB [32], PDSP K_i Database [33], and IUPHAR/BPS Guide to Pharmacology [34], with particular emphasis on off-target effects driving unexpected ADEs. Furthermore, the remaining qualitative drug-protein interactions were derived from CTD [24] and the above four sources to ensure comprehensive coverage of ADE molecular mechanisms. To further enhance the molecular foundation of personalized ADE prediction, PersADE integrated pharmacogenomic data from PharmGKB, encompassing genetic variants associated with 190 ADEs.

To validate the biological basis of organ-specific ADEs, PersADE integrated protein expression data from the Human Protein Atlas (HPA) database [35]. We systematically collected immunohistochemistry expression levels for 4699 ADE-associated proteins across 14 distinct organ systems, including brain, liver, kidney, gastrointestinal tract, and other

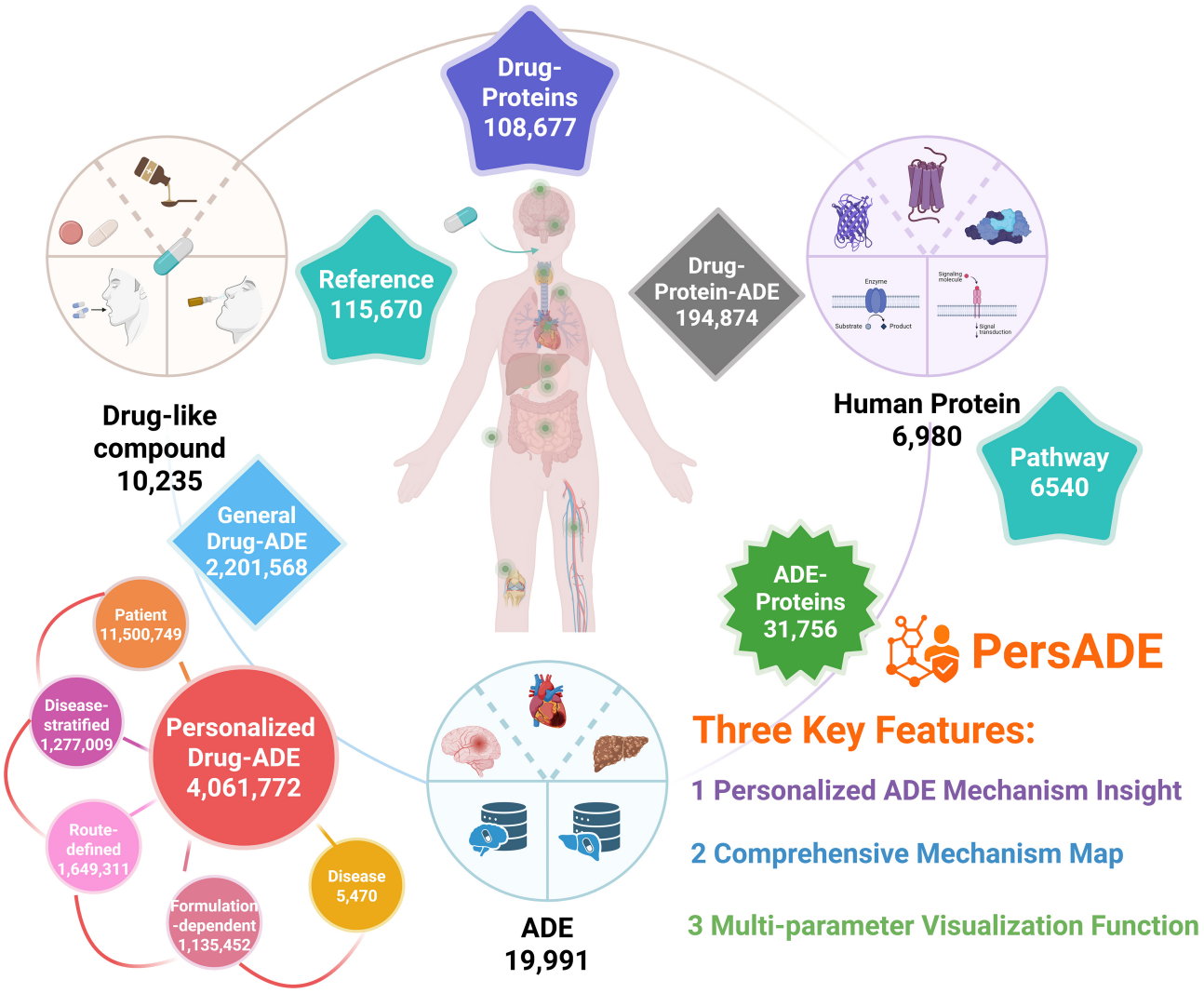

Figure 1. PersADE integrating the patient-level contexts, ADE annotations, drug properties, and associated human proteins to elucidate the underlying molecular mechanism. PersADE is unique in its comprehensive molecular mechanistic mapping, its personalized ADEs mechanism insight, and its multi-parameter visualization function. Created in BioRender. yu, z. (2025) https://BioRender.com/0oi6d0h.

major tissues. Through systematic mapping of 6 980 ADE-associated proteins to 348 KEGG pathways [28] and 6 191 MSigDB functional gene sets [29], multi-scale mechanistic resolutions were achieved spanning from individual molecular targets to complex biological networks. To ensure non-redundant pathway coverage, the MSigDB gene sets [29] specifically excluded all KEGG-derived pathways (C2:CP:KEGG subset). All these interactions are substantiated by 115 670 peer-reviewed papers, culminating in 194 874 drug-protein-ADE triplet associations that delineate the complete causal cascades from drug-target recognitions through pathway perturbation to clinical manifestations. Data standardization and knowledge enhancement further ensure interoperability and extensibility of PersADE. All 10 235 compounds are uniformly identified by InChIKeys and annotated using physicochemical properties, pharmacokinetic parameters, and pharmacological classifications from DrugBank [36] and PubChem [37]. To ensure clinical authenticity, all ADEs underwent systematic review to exclude non-genuine ADEs such as accidental exposures, patient medication errors, and events unrelated to the drug. The resulting 19 991 clinically verified ADE terms are mapped to UMLS Concept Unique Identifiers with cross-references to MeSH. A total of 6980 human proteins utilize UniProt [38] accessions as their identifiers, linked to protein domains, subcellular localizations, and Gene Ontology. Integration of KEGG pathway [28] and MSigDB gene sets [29] facilitates functional enrichment analysis and pathway perturbation research. In summary, these systematic standardization strategies ensure data consistency and completeness while establishing a robust foundation for downstream personalized ADE prediction and mechanistic inference.

Personalized Drug–ADE associations

PersADE offers a three-tier framework for personalized ADE analyses, systematically capturing complex interactions among individual, drug, and phenotype granularities to support data-driven individualized drug safety measurements. The foundation of personalization of PersADE resides in its comprehensive individual granularity module, which systematically captures and analyzes patient-specific factors affecting drug response, including basic data such as age, sex, weight and height, to construct detailed patient profiles that

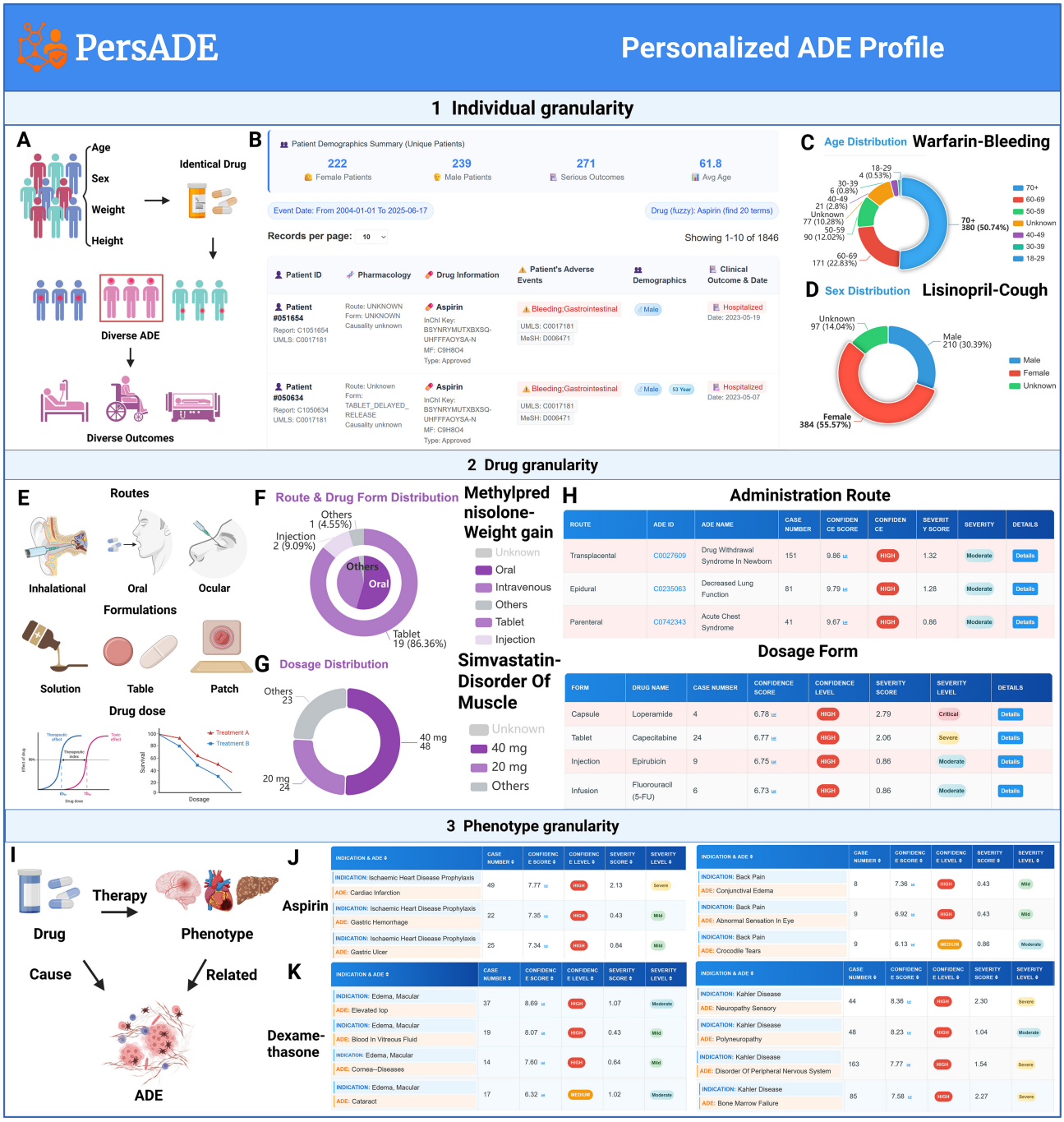

Figure 2. PersADE framework for personalized ADE profiling. The system has incorporated three granularity levels: individual, drugs and phenotypes. (**A**) Individual factors (age, sex, weight, and height) influence ADE susceptibility. (**B**) Patient demographics interface with real-time ADE illustration. (**C**) Age-stratified warfarin-bleeding incidence. (**D**) Sex-based lisinopril-cough distribution showing three-fold higher female incidence. (**E**) Drug administration route and formulation with dose–response relationship. (**F**) Methylprednisolone weight gain comparing oral versus intravenous route. (**G**) Dose-dependent simvastatin myopathy risk. (**H**) Interactive interfaces for drug safety parameter retrieval. (**I**) Phenotype module linking drugs, indications, and ADEs. (**J**) Aspirin ADE profile across cardiovascular versus anti-inflammatory use. (**K**) Dexamethasone ADE patterns in macular edema versus multiple myeloma treatment. Created in BioRender. yu, z. (2025) https://BioRender.com/0oi6d0h.

reveal how individual characteristics affect ADE susceptibility (shown in Fig. 2A). Through real-time visualization and demographic summary tables, this module displays demographic distributions and their correlation with specific adverse events, moving beyond simple frequency counts to facilitate analysis of the mechanistic relations between patient characteristics and drug safety outcomes (described in Fig. 2B). This granular analysis gives key insights: age distribution reveals age-specific ADE susceptibility – for instance, warfarin-related major bleeding exhibits distinct age stratification, with the greatly higher annual incidence rates in older patients compared to younger elderly patients [39] (shown in Fig. 2C). Sex-based analysis demonstrates differences in drug response between male and female patients, as exemplified in randomized double-blind trials where the incidence of cough in female patients taking lisinopril (12.6%) was three times that of male

patients (4.4%) [40] (given in Fig. 2D). This fine-grained patient analysis enables the identification of different ADE patterns leading to varied clinical outcomes, ranging from minor events to severe results requiring hospitalization.

Building upon this patient data foundation, the drug granularity module of PersADE provides new insights into the impact of drug administration parameters on safety outcomes (offered in Fig. 2E). This module systematically analyzes 52 categories of administration routes, including oral, intravenous, inhalation, ocular, and transdermal delivery methods. Each route exhibits unique pharmacokinetic properties that directly influence the ADE patterns – for example, intravenous injection may trigger acute reactions due to rapid peak concentrations, while transdermal patches may cause local skin reactions. Similarly, the module categorizes dosage forms (such as solutions, tablets, and transdermal patches) and documents their distinct safety characteristics. For instance, when treating West syndrome, the incidence of weight gain in the oral prednisone group (75.9%) was greatly higher than in the intravenous methylprednisolone group (16.1%), potentially related to the longer bioavailability and systemic exposure time of oral formulations [41] (illustrated in Fig. 2F). Moreover, this database maintained continuous dose data, enabling complex dose-response relation analysis that allows clinicians to determine precise thresholds where therapeutic benefits transition to unacceptable risk. For example, the risk of myopathy with simvastatin monotherapy shows a clear dose-dependence: about 0.03% incidence at 20 mg and 0.08% at 40 mg (offered in Fig. 2G). The interactive visualization components display the effects of administration routes and dosage forms on adverse event patterns through the multidimensional charts from both drug and adverse event perspectives, while the structured query interfaces support clinicians in rapidly retrieving specific drug safety parameter combinations to enable evidence-based individualized medication decisions (depicted in Fig. 2H). In summary, the drug granularity module of PersADE gives a tool for evaluating and optimizing drug treatment regimens through a systematic integration of multidimensional parameters, including administration routes, dosage forms, and doses.

PersADE reveals actual conditions of patients through its phenotype granularity module, which establishes associations among drugs, therapeutic indications, disease phenotypes, and adverse events, capturing the complex clinical reality and analyzing how disease states affect drug safety (demonstrated in Fig. 2I). This module employs standardized medical coding systems to link therapeutic uses with specific phenotypes, documenting how disease states influence drug safety profiles. Taking Aspirin as an example, in cardiovascular prevention it primarily causes upper gastrointestinal disorders, mild bleeding tendencies, and occasional hemorrhagic strokes; when adopted for anti-inflammatory analgesia, the adverse event spectrum changes, with increased gastrointestinal bleeding risk accompanied by tinnitus (30%), peripheral edema, and eye disease risks related to long-term use [42, 43] (as shown in Fig. 2J). Dexamethasone in short-term use for macular edema primarily leads to elevated intraocular pressures (25–35% requiring pressure-lowering medications) and cataract formation (67.9% three-year incidence in phakic eyes); while in long-term use for multiple myeloma, it results in several ADEs including psychiatric symptoms (5–10%, mainly mood swings and insomnia) and increased risk of osteonecrosis [44, 45] (shown in Fig. 2K). This distinction is particularly valuable for patients with different diseases, as disease states create a unique physiological environment that can greatly alter drug response and safety. The phenotype module's color-coded confidence indicator and association strength metric provide immediate visual assessment of disease-specific risks, supporting rapid clinical decision-making in complex patient scenarios. Through integration of data across three granularity levels, PersADE provides a multidimensional patient risk assessment tool for clinical decision-making. The system presents multidimensional data through visualization interfaces and structured tables, documenting interactions among patient characteristics, drug properties, and disease contexts, supporting the treatment plan development using the individual characteristics, and helping to minimize patient-specific adverse event risks while optimizing therapeutic outcomes.

Comprehensive molecular mechanistic mapping for Drug-ADE association

PersADE establishes a comprehensive causal relationship analysis from molecular interactions to clinical phenotypes through constructing a four-dimensional mechanistic cascade framework (illustrated in Fig. 3A). It established a complete mapping system of "drug → protein → ADE phenotype → biological pathway," integrating drug-protein binding affinity and potential binding site data, tracking pathophysiological processes triggered by protein functional alteration, mapping to specific ADE phenotypes, and ultimately localizing regulatory effects to key signaling pathways. To ensure the reliability of mechanistic inferences, PersADE developed a comprehensive multi-perspective evaluation framework that fully characterizes drug-protein-ADE ternary associations across multiple dimensions including mechanistic analysis, confidence levels, and ADE organ specificity. In the mechanistic analysis dimension, PersADE systematically explores the multi-target spectrum underlying interconnected ADEs, systematically revealing the molecular basis of complex ADEs. The advantage of this module lies in identifying and quantifying synergistic effects among multiple targets, transcending traditional single-target analysis paradigms. Taking Cisapride as an example, this module successfully elucidated its multi-ion channel interference network through combined blockade of KCNH2, SCN5A, and KCNQ1, clarifying the molecular mechanisms of QT interval prolongation and arrhythmias, providing crucial guidance for drug safety assessment and structural optimization [46–49], as shown in Fig. 3B. In the confidence level dimension, PersADE annotates ternary associations into three tiers based on over 115 000 papers: "Valid" indicates that drug-ADE, protein-ADE, and drug-protein associations originate from the same study; "High" indicates that two of the associations share the same source; "Medium" indicates that the three associations are independently supported by separate literature, ensuring the credibility of mechanistic inference (shown in Fig. 3C). In the organ specificity dimension, PersADE systematically maps drug-target-organ three-dimensional associations through the ADE Tree Number classification system, covering 13 organ-specific ADE categories across 14 protein-expressing organ systems (provided in Fig. 3D). Leveraging protein expression data from the HPA, this analysis validates the mechanistic basis of organ-specific ADEs by confirming tissue-specific protein expression patterns. This organ-specific analysis not only helps identify tissue-selective toxicity of drugs but, more importantly,

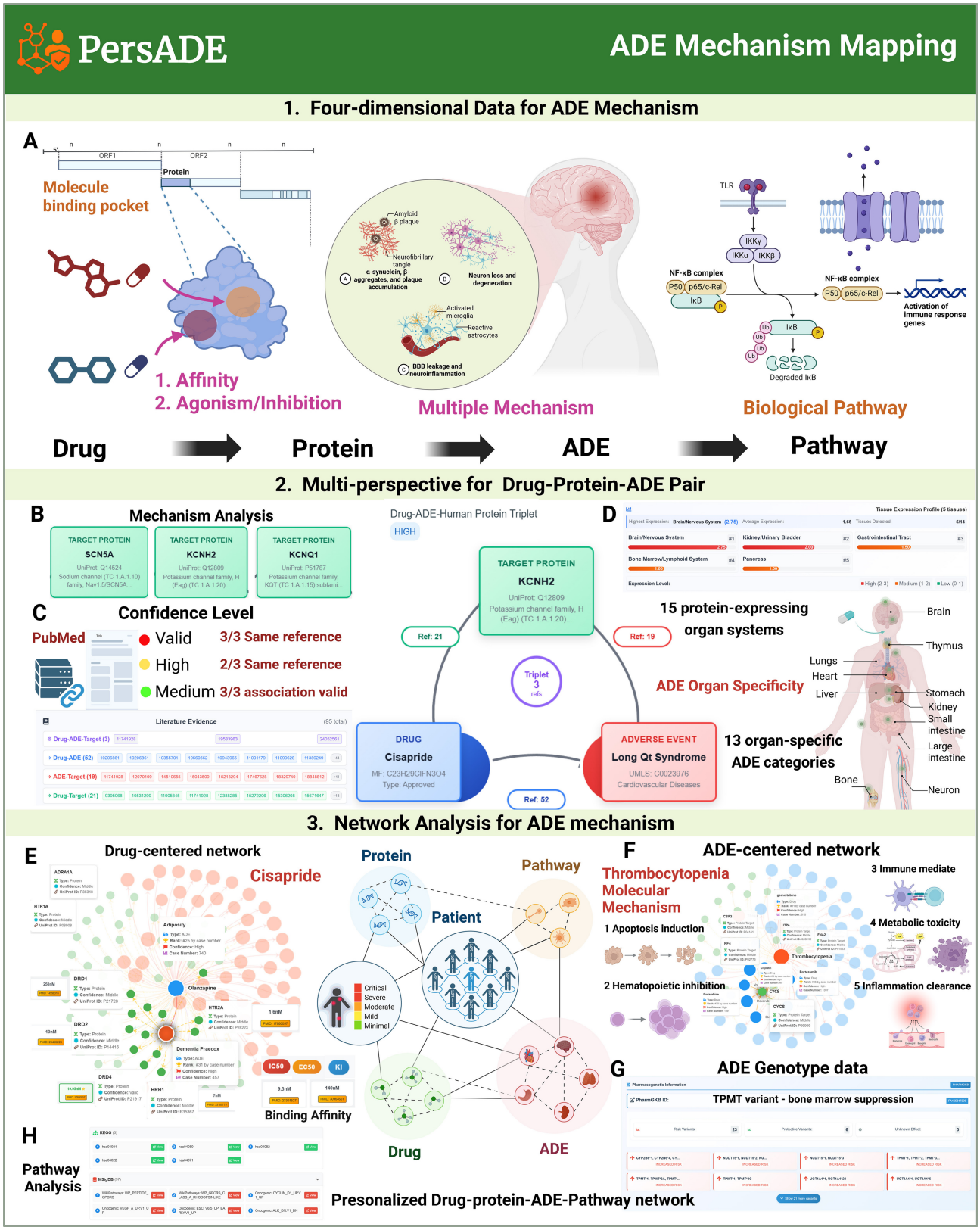

Figure 3. PersADE mechanistic framework for ADE analysis. (**A**) Four-dimensional cascade: drug → protein → ADE → pathways mapping with binding affinity and mechanistic data. (**B**) Cisapride multi-ion channel blockade (KCNH2, SCN5A and KCNQ1) causes cardiac arrhythmias. (**C**) Three-tier confidence system: Valid (same reference), High (2/3 same reference), and Medium (independent validations). (**D**) Organ-specific ADE mapping across 13 organ-specific ADE categories and 15 protein-expressing organ systems. (**E**) Drug-centered network providing multi-target profiles with binding affinities. (**F**) ADE-centered network exemplified by thrombocytopenia mechanisms. (**G**) Integration of pharmacogenomic data for genotype-stratified ADE risk assessment. (**H**) Pathway-level analysis for systematic safety assessment. Created in BioRender. yu, z. (2025) https://BioRender.com/0oi6d0h.

reveals the intrinsic connection between target expression patterns and ADE organ distribution. For instance, KCNH2, primarily expressed in cardiomyocytes, results in cardiac-specific ADEs (QT prolongation and arrhythmias) when blocked by agents such as Cisapride [48] and Terfenadine [50]; conversely, HRH1, widely expressed in the central nervous system, cardiovascular, respiratory, and gastrointestinal systems, causes multi-organ systemic reactions including drowsiness (central), tachycardia (cardiac), dry mouth (salivary glands), and constipation (gastrointestinal) when antagonized by the agents like diphenhydramine [51]. This refined organ-target mapping offers critical guidance for predicting tissue-specific risks of drugs and optimizing dosing regimens.

The network analysis module of PersADE achieves systematic mining of ADE mechanisms through constructing multi-level, multi-centered biological networks. The drug-centered network module (illustrated in Fig. 3E) innovatively integrates multi-dimensional drug-target interaction data, including binding affinity (IC_{50}, EC_{50} and K_i), action types (agonist, antagonist and inhibitor), and effect mechanisms (binding, activity and expression), offering a panoramic view for understanding complex ADE mechanisms. The advantage of this module resides in quantitatively characterizing drug multi-target effect profiles. Taking antipsychotic *olanzapine* as an example, network analysis integrating quantitative affinity and multi-receptor mechanism-induced seizures reveals: high-affinity antagonism of D2-like receptors (DRD2/3/4, K_i = 10–20 nM) forms an imbalance with low-affinity DRD1 (K_i = 250 nM), disrupting the inhibitory regulation of cortical-basal ganglia circuits [52, 53]. Ultra-high affinity antagonism of HTR2A (K_i = 1.6 nM) and HTR6 (K_i = 5 nM) directly increases cortical excitability, constituting core mechanisms of seizure risk [54]. HRH1 blockade (K_i = 1.2 nM) further weakens the antiepileptic protective effects of histaminergic and noradrenergic systems [46]. This multi-system synergistic effect explains the dose-dependent seizure risk of olanzapine, providing the molecular basis for high-risk patient identification. Furthermore, network analysis clearly demonstrates this complex "one drug-multiple targets, multiple targets-one effect" association: HTR2C antagonism increases appetite, HRH1 blockade reduces energy expenditure, HTR2A antagonism disrupts glucose metabolism, and ADRA1A antagonism limits lipolysis, forming a full metabolic syndrome-inducing network [46]. This multi-target synergistic action from central appetite regulation to peripheral energy metabolism highlights the systemic mechanism of severe obesity caused by antipsychotics, helping to discover ADE mechanisms.

The ADE-centered network module (offered in Fig. 3F) focuses on multi-factorial pathogenic mechanisms of specific ADEs, constructing reverse mapping networks from ADE-protein-drug, tracing from clinical phenotypes back to specific molecular mechanisms. Taking drug-induced thrombocytopenia as an example, PersADE integrates molecular mechanisms of 126 thrombocytopenia-inducing drugs, identifying major pathogenic mechanism categories: (a) apoptosis induction mechanism: cisplatin and fludarabine activate the caspase cascade via CYCS release [55, 56]; (b) hematopoietic suppression mechanism: gemcitabine and bortezomib regulate IFNA2 to inhibit megakaryocyte maturation, leading to 50–70% down-regulation of TPO receptor [57, 58]; (c) immune-mediated mechanism: heparin–PF4 complex activates the FcγRIIA receptor [59]; (d) metabolic toxicity mechanism: ITPA gene mutation patients display increased risk with thiopurine drugs [60]; (e) inflammatory clearance mechanism: CSF2/GM-CSF activation induces macrophage phagocytosis.

The integration of pharmacogenomic data further enhances personalized ADE prediction by incorporating genetic factors that influence drug response and toxicity susceptibility (shown in Fig. 3G). For example, TPMT (thiopurine methyltransferase) variants significantly affect thiopurine-induced bone marrow suppression, with homozygous variant carriers (TPMT2, TPMT3A, TPMT3C) showing increased toxicity risk compared to wild-type individuals [61]. PersADE integrates such pharmacogenomic associations from PharmGKB [14], enabling clinicians to stratify ADE risk based on patient genotype and adjust dosing regimens accordingly [62, 63]. This genotype-phenotype correlation approach transforms traditional population-based safety assessment into precision pharmacovigilance tailored to individual genetic profiles. These mechanistic analyses not only reveal molecular heterogeneity of the same ADE but also realize individualized risk stratification: combining patient demographic characteristics, clinical phenotypes, genotype information and medication parameters to reduce ADE risk, providing a molecular basis for precision prevention strategies and mechanism-based therapeutic decisions.

Moreover, this framework constructs a multi-level target-pathway-ADE association network via systematically mapping drug targets to biological pathway hierarchies. It can identify pathway affiliations of individual targets, attempting to elucidate the molecular mechanism by which drug perturbations produce systemic ADEs through complex signal network transduction. This integrated analysis strategy based on target pathway attribution enables PersADE to explain at the mechanism level why structurally diverse drugs produce similar clinical phenotypes, while also providing a computational framework for pathway feature-based drug safety assessment (as shown in Fig. 3H). Ultimately, PersADE constructs a complete causal chain from molecular interactions to clinical phenotypes through integrating the four-dimensional mechanistic cascade framework, multi-perspective confidence measurements, and multi-level network analysis. This system assesses multi-target synergistic effects, organ-specific risk and pathway-level mechanism, transforming traditional ADE records to a computable molecular mechanism network. By elucidating the complicated pattern of "one drug-multiple targets, multiple targets-one effect," our PersADE has established a computational way of measuring drug safety.

Drug-ADE association confidence and safety score

Based on massive personalized drug-ADE associations and detailed patient profiles, PersADE constructed a quantitative grading system for ADEs to assess the degree of drug-ADE association and their risk stratification for patients. Regarding association assessment, PersADE precisely quantifies drug-ADE associations by integrating three core dimensions: statistical significance, reporting ratios, and clinical evidence. This platform employs Fisher's exact test combined with Bonferroni correction to assess statistical significance, integrates two disproportionality measures comprising the Reporting Odds Ratio (ROR) and Proportional Reporting Ratio (PRR) to measure association strength, and evaluates clinical evidence strength based on case report counts (offered in Fig. 4A). Through a five-step cascade processing workflow that encompasses raw score calculation, association strength integration,

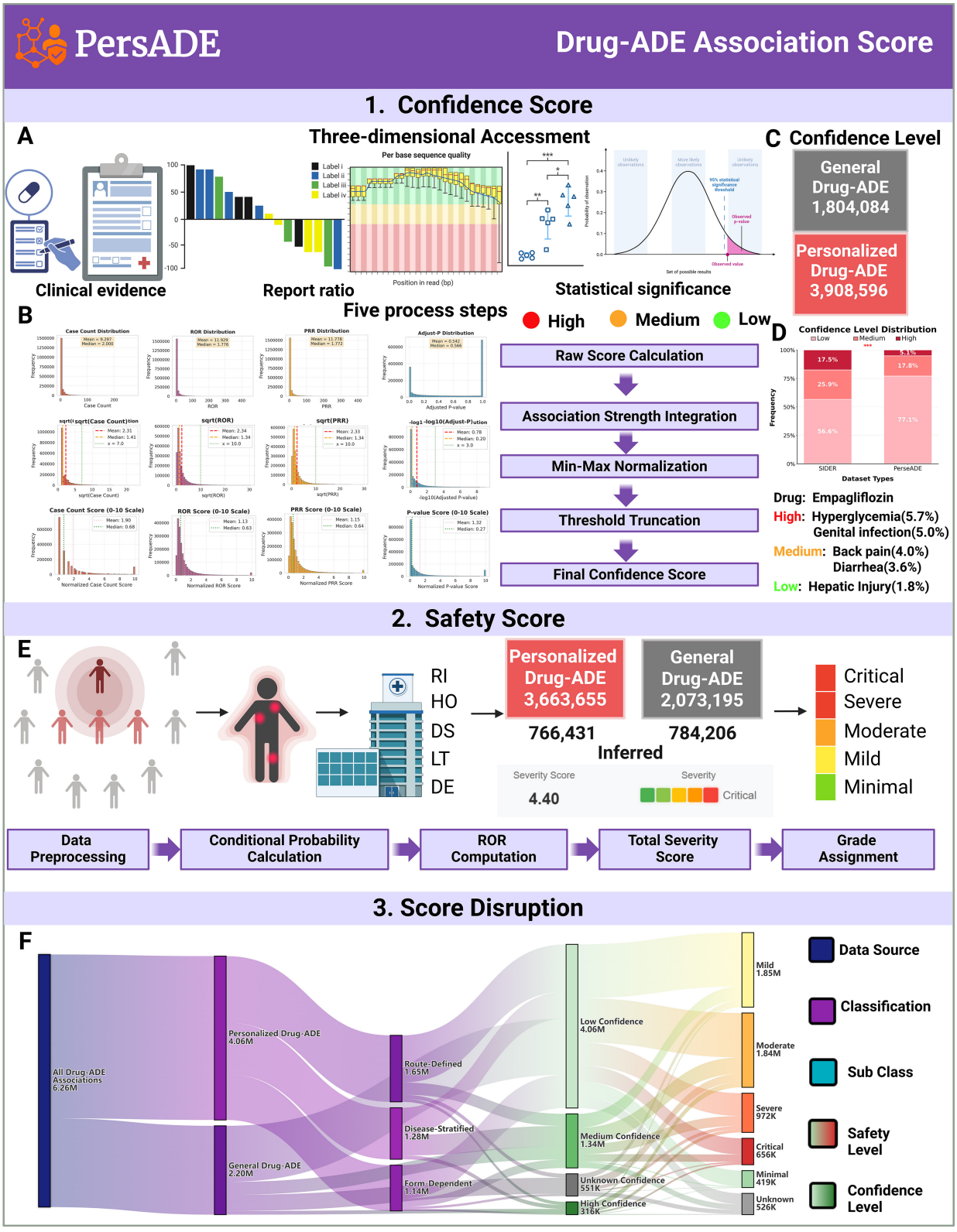

Figure 4. PersADE dual-dimensional scoring framework for drug–ADEs associations. (**A**) Three-dimensional confidence assessment integrating clinical evidence, reporting ratios, and statistical significance. (**B**) 5-step confidence score workflow with distribution transformations at each stage. (**C**) Classifying the 4.06M personalized and 2.20M associations into high/medium/low confidence levels. (**D**) confidence level distribution breakdown by dataset types (SIDER vs PersADE). (**E**) Severity assessment pipeline mapping personalized association to diverse grades (Critical to Minimal) based on patient outcome. (**F**) The Sankey diagram depicts the hierarchical distribution of 6.26M associations among personalized dimension, confidence level (Low 64.1%, Medium 21.4%, High 5.3%), and safety grades. Created in BioRender. yu, z. (2025) https://BioRender.com/0oi6d0h.

min-max normalization, threshold truncation, and final confidence score generation, PersADE standardizes scores across all dimensions to a 0–10 scale (depicted in Fig. 4B), combined with automatic filtering of invalid signals and vectorized computational optimization. The distribution characteristics of each dimension are found: case counts follow a long-tail distribution, ROR and PRR exhibit a similar left-skewed distribution, while the adjusted p-values show a bimodal distribution. As described in Fig. 4C, the platform classifies 3 908 596 personalized and 1 804 084 general drug-ADE associations into high, medium and low confidence levels. This successfully achieves the transition from traditional binary judgment to continuous confidence scoring, offering a tool for assessing personalized pharmacovigilance. To validate our confidence scoring framework, we conducted two complementary validation analyses. We compared confidence score distributions of PersADE against SIDER. The confidence level stratification showed significant differentiation ($p < 0.001$, t-test) and contains proportionally more high-confidence associations (17.5%) compared to our comprehensive dataset (5.1%) (shown in Fig. 4D). However, the number of high-confidence associations in PersADE (92 406) far exceeds SIDER (14 462). To further validate the clinical applicability of the confidence scoring framework, we examined empagliflozin, a widely-prescribed SGLT2 inhibitor, comparing our confidence scores against safety data from comprehensive clinical trials involving over 15 000 patients with type 2 diabetes [64]. The results demonstrated strong concordance with reported clinical frequencies. High confidence scores accurately identified common ADEs, including genital infections (5.0% incidence, score: 8.65) and hyperglycemia (5.7% incidence, score: 7.29). Medium confidence scores appropriately captured events with moderate frequency, such as back pain (4.0% incidence, score: 3.33), diarrhea (3.6%, score: 3.33), and arthralgia (2.9%, score: 3.33). Notably, our system correctly assigned low confidence scores to rare but serious events like breast cancer (0.1% incidence, score: 1.99) and hepatic injury (1.5%, score: 1.45), which validates the clinical relevance of our quantitative framework across different therapeutic classes.

For severity assessment, PersADE quantitatively assesses ADEs' clinical impacts by integrating three key elements: outcome weights, conditional probabilities, and reporting odds ratios (shown in Fig. 4E). The severity assessment module assigns differentiated weights ranging from 1 to 5 and corresponding penalty factors from 5 to 1 using five patient outcome categories: required intervention to prevent impairment (RI), hospitalization (HO), disability (DS), life-threatening conditions (LT), and death (DE). It calculates outcome distributions for drug-ADE combinations through conditional probability P(Outcome|Drug, ADE, X) and adjusts association strength by ROR value. By a five-step computational process – data preprocessing, conditional probability calculation, ROR computation, comprehensive severity score generation, and grade assignment – the system employs logarithmic transformation to integrate multidimensional parameters into a unified severity score. The severity score formula balances the contribution of outcome severity, occurrence probability, and statistical significance. It should be displayed as follows.

$$\text{Severity Score} = \frac{\sum W_k \times P_k}{\log_2 Pen_k \times \left(1 + e^{-\log_2 ROR}\right)}$$

Where k denotes the five outcome types (RI, HO, DS, LT, DE); W_k indicates the weight assigned to outcome k; P_k shows the conditional probability of outcome k occurring, Pen_k presents the penalty factor for outcome k. The platform ultimately maps 3 114 148 personalized drug-ADE associations to a five-tier severity system as follows: Minimal, Mild, Moderate, Severe and Critical, achieving the transition from traditional qualitative grading to precise quantitative assessment. By combining clinical outcome data with statistical methods, this framework provides scientific evidence for precise risk stratification and clinical decision support in drug safety. Furthermore, we implemented two complementary inference methods based on molecular and semantic similarity principles to enhance the coverage of safety assessments. For drug-ADE pairs lacking direct safety scores, we applied a molecular similarity-based inference approach using MACCS fingerprints and Tanimoto coefficients (threshold $\geq$0.7), enabling weighted averaging of safety scores from structurally similar compounds. Similarly, for ADEs with limited scoring data, we employed semantic similarity weighting based on UMLS ontological relationships, inferring safety scores through weighted averaging of semantically related ADEs. This dual-pronged approach significantly enhanced the completeness of our safety assessment framework. This method expanded safety scoring coverage by 1208 additional ADEs.

PersADE visualizes the hierarchical assessment pathway of 6.26 million drug-ADE associations through a Sankey diagram (given in Fig. 4F). Personalized associations are subdivided across 3 dimensions: route of administration with 1.65 million route-defined associations, formulation with 1.14 million form-dependent associations, and drug indication with 1.25 million disease-stratified associations. Confidence levels give a pyramidal distribution: low confidence dominates at 4.06 million associations (64.1%), followed by medium confidence at 1.34 million associations (21.4%), while high confidence accounts for 0.32 million associations (5.3%). For safety grading, we implemented similarity-based inference methods leveraging molecular fingerprint similarity for drug-ADE pairs and semantic similarity for ADE relationships to achieve substantially improved coverage: route-defined associations increased to 1.53 million (0.38 million inferred), formulation-dependent associations reached 1.00 million (0.30 million inferred), and disease-stratified associations expanded to 1.13 million (0.09 million inferred). The resulting safety grade distribution reveals that severe and critical risks requiring priority monitoring constitute 26.0%, moderate risks account for 29.4%, while mild and minimal risks predominate at 36.2%. Notably, the implementation of inference methods reduced associations classified as 'unknown' due to insufficient clinical outcome data from 34.1% to 8.4%, significantly enhancing the practical utility of safety assessments. This multi-dimensional assessment system enables clinicians to perform precise risk-benefit evaluations based on evidence strength and potential harm severity, with high confidence-high severity associations serving as primary references for clinical decision-making.

Multi-parameter search and Multi-page visualization

The PersADE database employs a relational database architecture, constructing a structured data model centered on four essential entities: patients, drugs, adverse events, and proteins. Through meticulously designed association tables, the system captures the complex relationship networks among these enti-

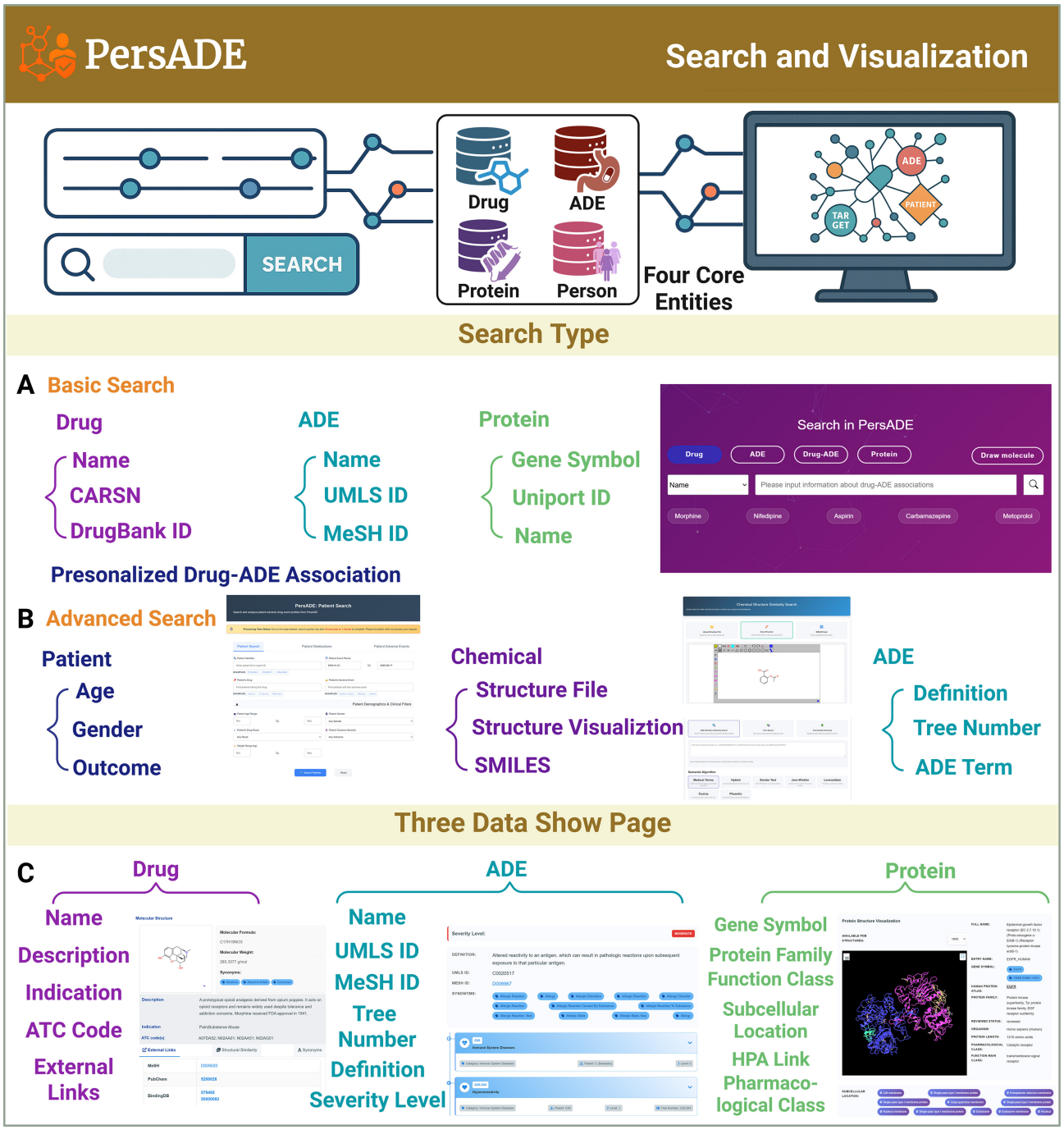

Figure 5. PersADE search interface and visualization architecture. (**A**) The basic search supports standardized identifiers for drugs (generic names, CARSN and DrugBank IDs), ADEs (UMLS ID, MeSH ID), and proteins (gene symbol and UniProt ID). (**B**) advanced search with patient-specific filtering, chemical structure similarity search via JSME editor and ADE semantic search. (**C**) entity-centric display pages showing drug information (ATC codes and indications), ADE data (medical coding and severity level) and protein annotation (subcellular localization and 3D structure). The system enables multidimensional exploration of personalized drug–ADE associations. Created in BioRender. yu, z. (2025) https://BioRender.com/0oi6d0h.

ties, with composite indices established on key search fields to ensure efficient storage and retrieval of large-scale drug safety data (shown in Fig. 5A). This architecture not only ensures data integrity and consistency but also establishes a foundation for multidimensional ADE analysis. PersADE implements a unified search portal that accommodates diverse query types through specialized modules, addressing the multidimensional nature of ADE research. The basic search interface supports both text-based queries and structured searches with real-time suggestions. Drug searches utilize generic names, CAS numbers, and DrugBank identifiers, with fuzzy matching implemented specifically for drug names to accommodate variations and common misspellings. Adverse events are indexed using MeSH terminology with fuzzy search capabilities for ADE terms, complemented by UMLS standards for semantic expansion. Protein information employs gene symbols and UniProt identifiers, with fuzzy matching available for target names (depicted in Fig. 5B). This targeted implementation of

fuzzy search for nomenclature-based queries, combined with exact matching for quantitative and categorical parameters, balances search flexibility with precision.

The advanced search functionality showcases the chance for exploration personalized medicine, and molecular analysis. The patient risk assessment module revolutionizes ADE prediction through demographic and clinical filtering, including age ranges, sex specifications, weight parameters, and drug administration routes, enabling precise patient cohort definition and personalized risk profiling via integrated analysis of patient medications, adverse events and temporal relations. The structure search module integrates JSME [65], supporting a direct structure drawing or SMILES input, with three fingerprint algorithms, FP4, FP3, and FP2, optimized for different similarity aspects. Adjustable Tanimoto coefficient threshold facilitates identification of structurally related compounds with potentially similar ADE profiles. For ADE retrieval, it employs complementary semantic search algorithms, including Medical Terms matching, natural language processing and ADE definition similarity measures. Combined with the ADE ontology tree and adjustable similarity thresholds, these abilities support flexible mapping for diverse ADEs (shown in Fig. 5C).

In terms of data presentation, our database uses an entity-centric three-page information architecture that displays multidimensional attributes of each core entity (shown in Fig. 5D). The drug page integrates ATC classifications, diseases, detailed pharmacological descriptions, and authoritative external database links, constructing a complete drug knowledge system. The adverse event page provides standardized medical coding while incorporating a clinical severity grading system, offering a quantitative basis for drug risk-benefit assessment. The protein page provides in-depth annotations from a molecular mechanism perspective, including subcellular localization, protein family affiliation, biological function classification, and pharmacological properties. Most protein entries include direct hyperlinks to the HPA database, providing users seamless access to detailed tissue expression profiles, immunohistochemistry images, and subcellular localization data to support organ-specific ADE analysis. This multi-layer information provides crucial insights for elucidating the biological basis of ADEs.

Conclusion

PersADE presented a database which systematically integrated personalized ADEs and their underlying molecular mechanisms. It encompassed over 4 million personalized drug-ADE associations, 32 000 protein-ADE associations, and 108 000 drug-protein interactions, with particular emphasis on off-target effects. Its features included the provision of demographic characteristics, disease contexts, and drug administration parameters relevant to ADEs, realizing a stratified analysis of drug-ADE association. Moreover, PersADE integrated interaction networks among drugs, human proteins and ADEs, providing mechanistic insights. By the construction of a four-dimensional mechanistic framework of "drugs → protein → ADE phenotype → biological pathway", PersADE achieves causal relationship analysis from molecular interactions to clinical phenotypes, thereby providing a tool for personalized drug safety assessment. Future integration of more genotype data will further advance PersADE toward comprehensive personalized ADE research, representing the next frontier in precision drug safety.

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Conflict of interest

None declared.

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Data availability

All data can be viewed, accessed and downloaded from PersADE, which is accessible without any login requirement by all users at: https://idrblab.org/PersADE.

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