Biomedicine & Pharmacotherapy 163 (2023) 114784

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

journal homepage: www.elsevier.com/locate/biopha

Review

Integrative toxicogenomics: Advancing precision medicine and toxicology through artificial intelligence and OMICs technology

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ARTICLE INFO

Keywords:
Toxicogenomics
Personalized medicine
Toxicology
Artificial Intelligence (AI)
Database

ABSTRACT

More information about a person's genetic makeup, drug response, multi-omics response, and genomic response is now available leading to a gradual shift towards personalized treatment. Additionally, the promotion of non-animal testing has fueled the computational toxicogenomics as a pivotal part of the next-gen risk assessment paradigm. Artificial Intelligence (AI) has the potential to provid new ways analyzing the patient data and making predictions about treatment outcomes or toxicity. As personalized medicine and toxicogenomics involve huge data processing, AI can expedite this process by providing powerful data processing, analysis, and interpretation algorithms. AI can process and integrate a multitude of data including genome data, patient records, clinical data and identify patterns to derive predictive models anticipating clinical outcomes and assessing the risk of any personalized medicine approaches. In this article, we have studied the current trends and future perspectives in personalized medicine & toxicology, the role of toxicogenomics in connecting the two fields, and the impact of AI on personalized medicine & toxicology. In this work, we also study the key challenges and limitations in personalized medicine, toxicogenomics, and AI in order to fully realize their potential.

1. Introduction

Personalized medicine and toxicology are two fields that are increasingly becoming interconnected [1]. Personalized medicine aims to optimize treatment outcomes by taking into account an individual's unique characteristics, such as genetics, lifestyle, and environment [2]. The field of toxicogenomics, which combines the study of genetics and the toxicological aspect of drugs/chemicals, plays an important role in connecting personalized medicine and toxicology. Personalized medicine is an emerging field that aims to provide the right treatment to the right patient at the right time, taking into account the patient's unique characteristics [3]. This approach is based on the recognition that no two patients are alike and that traditional "one-size-fits-all" approaches to treatment may not be effective for all patients [4]. Personalized medicine uses a combination of genetic, molecular, and clinical data to tailor treatment to individual patients. This can include genetic testing to identify patients who are at risk of certain diseases or to predict how they would respond to specific treatments. It also includes the use of molecular profiling to identify the specific characteristics of a patient's disease and to select the most appropriate treatment [5]. Since genetic makeup is one of the primary causes of cancer, diabetes, autoimmune diseases, pediatric diseases and behavioural disorders, personalized medicine is expected to be the future of such clinical problems. As the concept of personalized medicines indicates, the novelty or the personalization lies in the decision process towards a particular therapy, which in turn is handled based on a host of data across the population. It further proceeds to define the patient's or individual's response to a disease, based on integrated multi-omics information from different

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https://doi.org/10.1016/j.biopha.2023.114784
Received 7 March 2023; Received in revised form 15 April 2023; Accepted 24 April 2023
Available online 28 April 2023

aspects involving proteomics, genomics, epigenomics, transcriptomics, metabolomics, microbiomics and several other omics fields. The inclusion of an undeniable approach and disaggregation of data by sex and gender [6] has led to the possible inclusion of genderomics and sexomics which were often neglected in the past science. Accordingly, genomic and epigenomic signatures localize at the branch point among genome, phenome, and sexome in both health and disease conditions suggesting a multi-omics approach as the unique complete strategy [6]. Among the different applications of personalized medicine, genetic screening for diagnosis, and drug therapy for genetic markers of efficacy are commonly focused on by researchers. However, the integration of these efficacy markers needs proper evidence of clinical validity during all stages of individual treatment[7]. A proper understanding of drugs adsorption, metabolism and excretion along with their half-life is needed for each patient [8].

The field of toxicology is concerned with the identification, characterization, and quantification of the adverse effects of chemicals and other agents on living organisms [9]. This includes the study of the mechanisms of toxicity, the identification of susceptible populations, and the development of strategies for risk assessment and risk management. Personalized medicine is an important tool to be considered by toxicologists, as it is expected to reduce drug attrition and development process and time, improve safety assessments, and facilitate a better understanding of drugs' mechanisms of action. Recent paradigm shifts towards the application of alternate models for toxicity testing can be seen after the popularity to discontinue animal testing has peaked. In line with this, computational toxicology has emerged as a game-changer without its need to conduct testing on apical end points [10].

Considering the huge data obtained from omics applications and toxicological profiles, the impact of AI on these fields is becoming more and more relevant [11]. The advent of AI is expected to fuel changes to toxicogenomics and toxicology in the near future. Currently, many models and databases are being developed to amalgamate the field of toxicogenomics and toxicology to make the decision process of personalized medicine more systematic and time-efficient.

1.1. The role of toxicogenomics in connecting personalized medicine and toxicology

Toxicogenomics is the study of how a person's genetic profile may impact how they react to a specific medication. To comprehend how a person's genetic composition can alter their reaction to a specific treatment in response to various exposure scenarios of therapeutic agent uptake, this field merges the study of genetics and drug metabolism (Fig. 1). This can be applied to optimise drug dosage and lower the possibility of negative effects due to chemical exposure. For instance, some people may metabolize a drug differently than others due to genetic variances, necessitating a different dosage or alternative medication.

Toxicology and personalized medicine are connected through the use of toxicogenomics, which assists in determining how a person's genetic makeup can impact the reaction to a specific medication. Broadly, this field combines the study of genetics and drug metabolism to understand how an individual's genetic makeup can affect his/her response to a particular medication. This can be used to optimize drug dosing and reduce the risk of adverse reactions.

Another way toxicogenomics connects these two fields is by enabling genomic techniques to study the effects of chemicals and other agents on the genome and transcriptome, and how these effects enable predicting an individual's response to exposure. This aids in identifying individuals who may be at increased risk of adverse effects from exposure to a particular chemical or agent. Finally, Toxicology is also related to personalized medicine by identifying the risk of exposure to environmental toxins. It can also assist in reducing the risk of disease and improving the health outcomes. Overall, toxicology plays an important role in personalized medicine by providing information on how an

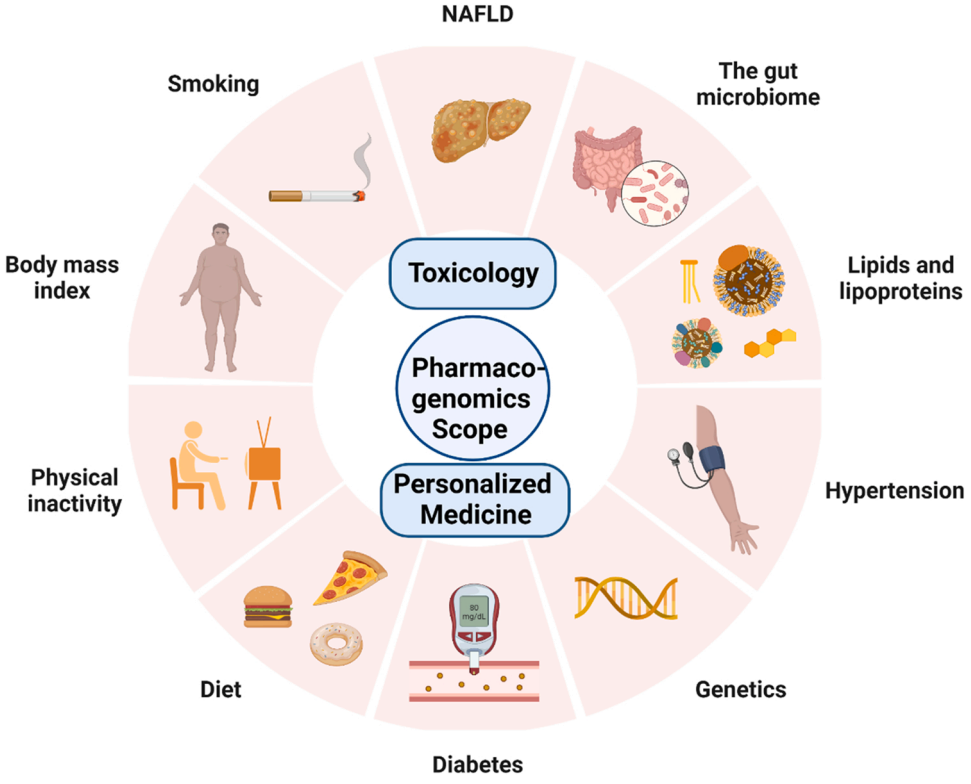

Fig. 1. Risk Assessment using Toxicogenomics. Use of toxicogenomics to predict an individual's susceptibility to toxicity from environmental pollutants or therapeutic drugs. By identifying genetic variations that affect the metabolism or detoxification of these compounds, risk assessment can be improved, and more effective interventions can be developed to protect vulnerable populations.

individual's unique characteristics can affect their response. Nowadays, merging classic and novel GWAS-identified genomic loci is mandatory for complete individual profile identification and risk assessment, especially for complex diseases and traits [12].

1.2. The impact of artificial intelligence and machine learning (ML) on personalized medicine and toxicology

Artificial intelligence is a rapidly growing field that has the potential to revolutionize personalized medicine and toxicology [13]. AI is a set of technologies that enable computers to simulate human intelligence and perform tasks that would typically require human intelligence, such as learning, reasoning, and decision-making. AI can be used to analyze large amounts of data and make predictions about treatment outcomes or toxicity. From a toxicologist and clinician's perspective, AI represents the applications of computational powers to resemble a human-like decision-making process. Many techniques including fuzzy expert systems, artificial neural networks, and machine learning are commonly applied in the medical application of AI [14]. In personalized medicine, AI assists in patient data analysis, such as genetic and molecular profiling data to predict treatment outcomes and select the most appropriate treatment for individual patients. AI can also be used to monitor disease progression, treatment response, and identify patients who may be at risk. Machine learning is commonly used in this regard with predictions backed by mathematical data points as supervised by humans. Alternatively, more unsupervised techniques have also been gaining popularity in the healthcare field in recent years [15]. Virtual applications of AI in healthcare can range from analyzing electronic health records to personalized medicine based on clinical genomics [16]. As can be observed in Fig. 2, AI applications involve the integration of several diverse data points contributed by time-driven patient chart monitoring blood pressure, heart rate, laboratory results, and others along with a series of medical images from x-rays, CT, MRI, and ultrasound [17–19]. An amalgamation of all these data into machine-understandable code to identify patterns in the patient response contributes to the decision-making process.

In toxicology, AI analyses complex data on the effects of chemicals and other agents on living organisms; this is achieved by the integration of cheminformatics and bioinformatics. With the availability of huge data in these fields, innovations with big data-based AI are expected to get incited [20]. This can help to identify potentially hazardous compounds and to prioritize them for further testing. AI can also be used to analyze large amount of toxicology data, such as from animal studies, identifying the patterns and predicting the toxicity in humans. AI could also assist to analyze large amount of data from toxicogenomic studies identifying genetic variations that are associated with drug response and developing decision-support tools for drug dosing and treatment selection. Currently, studies targeting the AI model development for toxicity prediction are more predominant. However, very limited studies exist that predict the toxicity mechanisms [20]. This can be attributed to the lack of scientific consensus on such AI-predicted mechanisms. Since AI is continuously and rapidly evolving, this is certainly in demand establishing standard models for toxicity predictions and mechanisms.

Despite the potential of AI in personalized medicine and toxicology, there are still some challenges that need to be addressed. These include the need for large amount of high-quality data, the need for robust and well validated algorithms to interpret the results. Additionally, there are concerns on the bias and discrimination in AI-driven approaches; thus, these approaches need to be transparent and interpretable.

2. Personalized medicine and toxicology: an overview

Toxicology and personalized medicine are intertwining. The personalized medicine seeks to improve treatment outcomes by considering the patient's particular traits including the genetics, lifestyle, and environment, [22]. Toxicology, in contrast, studies the effect of chemicals on living things; it also indicates the options to reduce the effects. We give an overview of these two topics in this section, outlining their definitions, concepts, present applications, and difficulties. The goal of personalized medicine is to give the appropriate medication to the appropriate patient at the appropriate time while taking into consideration the patient's features [6]. This strategy is founded on the understanding that no two people are the same and that conventional, "one-size-fits-all," approaches to treatment may not be successful for all patients [23]. In order to customize treatment for specific patients, personalized medicine combines genetic, molecular, and clinical data. Genetic testing can determine the patients those are at risk of developing a particular disease; it can too forecast how they would react to a particular course of treatment. Additionally, molecular profiling is used to determine the precise features of a patient's illness and the best therapeutic approach.

Many patients may not react favorably to the majority of medications, the precision medicine's goal is to overcome this. The precision medicine identifies the patients who should receive a certain treatment and the appropriate dosage. This is known as personalized medicine; it certainly widens the implementation domain. Thus, knowing the primary causes of heterogeneity is necessary in treatment response for the implementation of precision medicine.

Toxicology in personalized medicine is the study of the pharmacokinetic variability regarding a particular medication in a single patient. The causes of pharmacokinetic variability, particularly those connected to an individual phenotype and genotype, are typically well understood, and the prescription information addresses how they may affect a patient. Through population pharmacokinetics analysis and targeted studies that address typical reasons for pharmacokinetic variabilities, such as age, the presence of food, organ failure, and concurrent treatment, the impact of phenotype are thoroughly investigated for the majority of medications. Recently, it has been demonstrated that the microbiota influences pharmacokinetic variability [24]. For various medications whose absorption, distribution, metabolism, or elimination include polymorphic metabolic enzymes or transporters, the effect of genotype has also been studied.

Pharmacodynamic variability that frequently makes up the majority of response variability is significantly less derived than pharmacokinetic variability. When there are known target receptor polymorphisms, the subject genotype has been examined; nevertheless, there are relatively few instances, where this has resulted in recommendations that affect the selection of a medicine or dose.

Warfarin is the most well-known example; the polymorphisms in vitamin K epoxide reductase convertase 1 affect the sensitivity of the body and are taken into account, while designing the dosing algorithms [25,26]. Occasionally, a person's genotype identifies who should not receive a drug, such as in the cases of abacavir (HLA-B5701), carbamazepine (HLA-B1502), and simvastatin (SLCO1B1) [27] [28].

2.1. Current applications and challenges in personalized medicine and toxicology

Personalized medicine has the potential to revolutionize the way the disease is usually understood and treated. There are several current applications of personalized medicine in the clinic, including the use of genetic testing to guide treatment decisions, the use of molecular profiling to select the most appropriate treatment for individual patients, and the use of toxicogenomics to optimize drug dosing and reduce the risk of adverse reactions. The Human Genome Project, the International HapMap Project, and Genome-wide Association Studies (GWASs) are just a few of the molecular scientific breakthroughs that have helped medicine over the past ten years (International HapMap Consortium, 2005). Single nucleotide polymorphisms (SNPs) are already a great resource for mapping complicated genetic features because they are already acknowledged as one of the primary drivers of human genetic diversity and disease modulators [29].

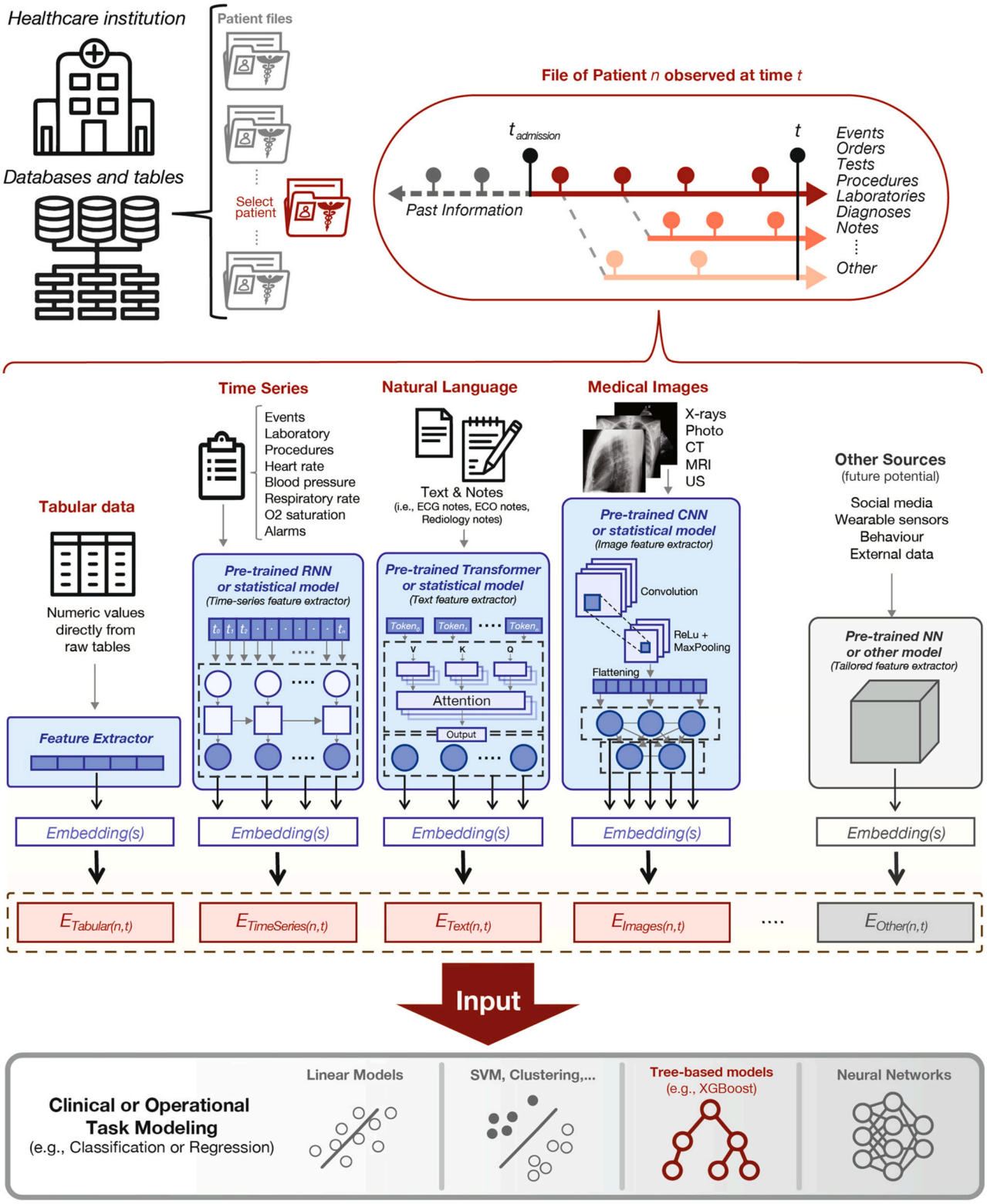

Fig. 2. Illustrating the Holistic Artificial Intelligence in Medicine (HAIM) framework which is used to process the databases and tables sourced from leading healthcare institutions. The framework processes the data to generate individual patient files which contain past and present multimodal patient information from the moment of admission. The data modality is fed to independent embedding-generating streams. The tabular data is minimally processed using simple transformations or normalizations to produce encodings or embedding-like categorical numerical values. The selected time series is processed by generating statistical metrics to produce embedding representative of their trends. Natural language inputs such as notes are processed using a pre-trained transformer neural network to generate text embeddings of fixed size. Image inputs such as X-rays are processed using a pre-trained convolutional neural network to extract fixed-size embedding. All generated embeddings are concatenated to generate a fusion embedding that can be used to train, test, and deploy models for predictive analytics in healthcare operations. Reproduced with permission[21]. Copyright 2022, Springer Nature.

However, some challenges need to be addressed to realize the full potential of personalized medicine. These include the need of high-quality data, robust and validated algorithms, and effective methods to interpret the results of personalized medicine-driven analyses. Microarray-based genotyping techniques, which could only examine regions of known variation, are being replaced by sequencing technologies as they become more widely available and more cost-effective [30]. These technologies' high error rates present substantial difficulties for applications, such as finding new variations. By utilizing hashing, prefix and suffix trees, or other heuristics, many packages, like BLAT, have been tailored for the alignment of short reads. However, reference sequence bias is still a problem for short-read assemblers, because reads, with more similarities to the reference sequence, are more likely to map than reads with valid differences. A recent review studies comprehensively to correctly monitor these alignments to prevent these problems [31].

Genetic changes can affect gene expression in complex ways, and many effects at different can be commonly expected. The development of diagnostic tools, the selection of pertinent variations for pharmacogenetic investigations, and the accurate interpretation of associations depend on the elucidation of at least the primary functional variants of each gene. The development of large collaborative biobanks with extensive medical sample information, available to researchers upon request. to study genotype-phenotype relationships is a challenge in this area as are improvements to *in silico* prediction tools and in vitro test systems that frequently result in contentious and unreproducible data [32].

At this time, it is uncertain to pick out the most effective solution to these issues. The appeal of pathway-oriented techniques is that they are hypothesis-driven. Their weakness, meanwhile, is a lack of understanding of biological gene networks. GWA permits the identification of cis- and trans-genetic determinants without the need for a hypothesis and, in theory, may account for the heritability of virtually any phenotype. Incomplete and inadequate SNP coverage (lack of causative mutations, issues with pseudogenes, etc.) and poor statistical approaches for revealing the "hidden heritability" underlying the most significant relationships enduring multiple testing corrections are the current limitations. However, new technologies have already and would probably continue to pose significant problems to fundamental research because it would be crucial to functionally test a vast array of discoveries and ideas.

Toxicology plays an important role in protecting human health and the environment by identifying and assessing the risks associated with exposure to chemicals and other agents. There are several applications of toxicology, including the development of strategies for risk assessment and risk management, the identification of susceptible populations, and the study of the mechanisms of toxicity. However, some challenges should be addressed; these include the need for large amount of high-quality data and robust systems for the assessment of the chemical toxicity [33].

The availability of data has altered and improved with the development of laboratory automation and the paradigm shift toward 21st Century Toxicology, focusing on adverse impact routes and understanding mechanisms of action. For instance, projects like ToxCast and Tox21 have generated publicly accessible bioactivity data for various endpoints using high throughput/high content tests for a large number of compounds [34]. Additionally, omics technologies used to screen alterations in genomes, proteomes, metabolomes, and other systems have generated a wealth of data (Fig. 3). Data from biomonitoring and epidemiology are also become easier to be obtained. In toxicology, there are several current applications of AI, such as predicting the chemical toxicity and toxicity of other agents based on their structure and properties. AI is also helpful in analyzing large amount of toxicology data, such as from animal studies, to identify the patterns and predict toxicity in humans. However, there are still some challenges that include the need for large amount of high-quality data, robust and well validated methods for risk assessment, and effective risk management strategies in protecting human health and the environment [35].

Big data sets for predictive toxicology are usually diverse and variable. This relates to the measurement errors and inherent variability of biological data, variability connected to various measuring techniques employed by various laboratories. Additionally, there are errors in the

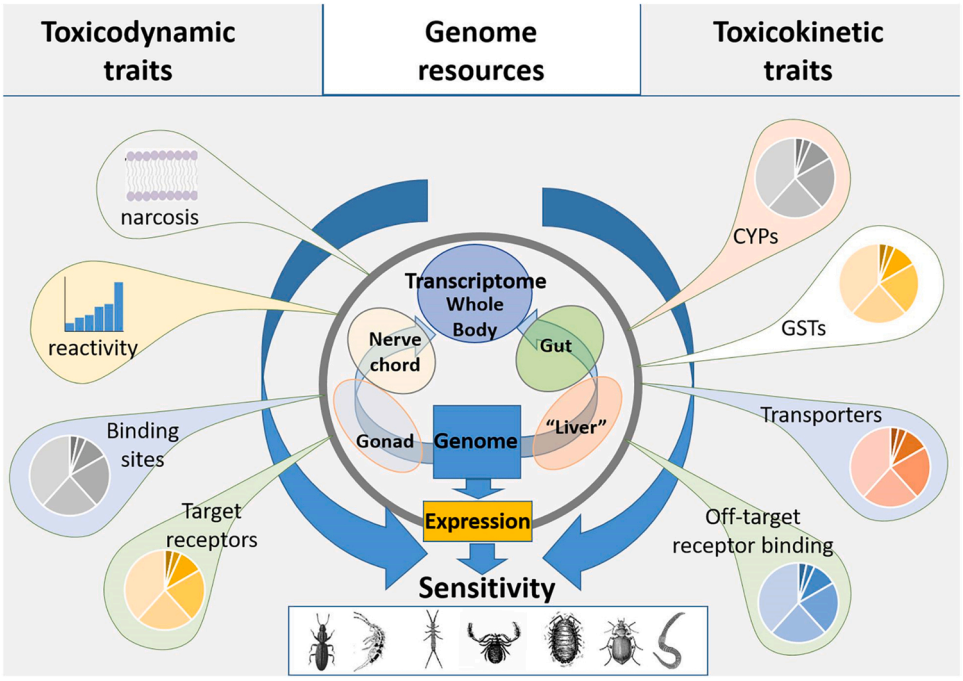

Fig. 3. Schematics show the Toxicokinetics (TK) trait inherent in a species, which may indicate the species' sensitivity to the absorption, distribution, metabolism and excretion of toxic substances. Toxicodynamics (TD) trait derived from genome resources, which may indicate a species' sensitivity to the toxic effects of a substance at the cellular and molecular level. Reproduced with permission [36]. Copyright 2020, Frontiers.

overall documentation and transfer of study results. The data sets are therefore subject to various types of uncertainties. It is equally necessary to improve the data quality, compatibility, and comparability of the data to reduce these uncertainties. The standardization of formats, agreement on the minimal data to be recorded for experimental data, and connection to standardized ontologies should all be pursued to overcome the challenges [37].

3. Toxicogenomics in personalized medicine and toxicology

The modern idea of personalized medicine is fundamentally based on pharmacogenetics, the study to know the effects on the genetic variation by drugs; toxicogenomics is the multifactorial extension of the same concept. Although a "personalized" approach has always been a hallmark of effective medical practice, toxicogenomics ensures the widespread use of molecular data to adapt medication therapy to each patient optimizing the therapeutic benefit and reducing the adverse events [38]. This can be used to optimize drug dosing and reduce the risk of adverse reactions. For example, individuals with certain genetic variations may metabolize a drug differently than others and may require a different dosage or a different drug altogether [26].

Over the past few decades, basic principles, and genes characterizing the absorption, distribution, metabolism and excretions (ADME) of drugs were accumulated resulting in huge data availability to fuel the current state of personalized medicined approaches. Toxicogenomics can play an important role in personalized medicine and toxicology by providing information about the individual's unique genetic makeup effect on the treatment and exposure to chemicals [39].

3.1. Drug development and therapeutic aspect of toxicogenomics

Toxicogenomics is supported by two major streams of research: 1) that seeks to understand the biological genotype-phenotype correlations and discover genetic variation, and 2) that builds on the former to look at genetic factors concerning the drug response phenotypes and use novel diagnostic tools translating this knowledge into clinical care. The speed and output of molecular discovery have been changed by modern technology providing us with new research tools. However, significant obstacles must be overcome to fulfil this promise for basic and clinical research. Toxicogenomics can be divided into several sub-disciplines, including pharmacokinetics, which focuses on the body mechanism to handle the drugs, and pharmacodynamics [40].

In drug development, toxicogenomics can identify genetic variations that may affect the drug response and select populations for clinical trials that are more likely to respond to the drug. This can help to optimize drug development and reduce the costs associated with clinical trials. Additionally, developing and verifying tests for potential therapeutic applications is of interest to the researchers. The first stage is to link the gene to the illness, then the researchers across the domains collaborate to find a chemical that may be altered to treat the ailment [41] (Fig. 4). Since we obtain a more precise understanding of diseases and the pharmacokinetics and pharmacodynamics of the new medicine, genetic advances have an impact on the creation of new drugs [41]. In therapy, toxicogenomics assists in optimizing drug dosing and reducing the risk of adverse reactions [42]. This can include the use of genetic testing to identify individuals at increased risk of adverse reactions to a particular medication, and the selection of alternative treatments that may be safer for these individuals.

3.2. Examples of pharmacogenomic-guided treatment in clinical practice

There are several examples of toxicogenomics-guided treatment in clinical practice. One example is the use of genetic testing to guide the use of warfarin, a blood thinner that is used to prevent blood clots. Warfarin is metabolized by several different enzymes in the body; genetic variations in these enzymes can affect the metabolism of warfarin and the risk of bleeding [43]. Genetic testing can be used to identify individuals at increased risk of bleeding and adjust the dose of warfarin accordingly. Another example is the use of genetic testing to guide the use of tamoxifen, a drug that is used to treat breast cancer. Genetic variations in the CYP2D6 enzyme can affect the metabolism of tamoxifen and the risk of recurrence [44]. Genetic testing enables the identification of individuals who may not be metabolizing tamoxifen effectively. This also enables the selection of alternative treatments that may be more effective for these individuals.

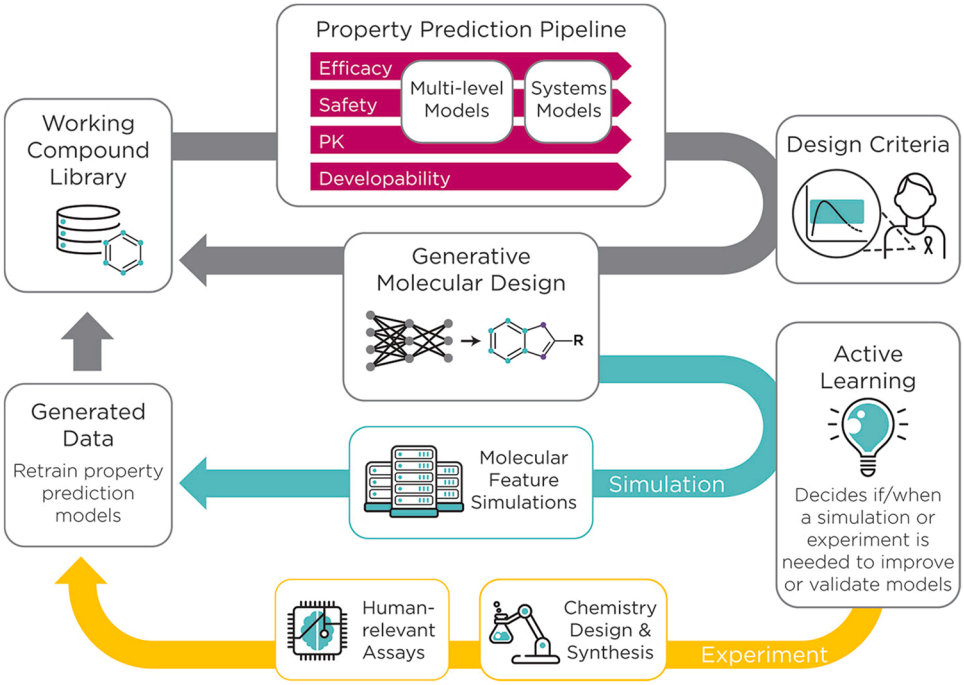

Fig. 4. The schematic is showing the workflow of preclinical drug discovery by applying a compound library as input for a property prediction pipeline. The pipeline starts by using historic data to train machine learning-based models for property prediction. It then integrates the multi-level and systems-level models for efficacy, safety, pharmacokinetics, and feasibility. This generates a set of drug design criteria that are simultaneously optimized for the generation of new molecules by the generative molecular design framework. The process can be repeated numerous times using an active learning approach to decide when a molecular simulation or experiment is needed to improve or validate the models. The result of this workflow is a set of optimized drug candidates [45].

3.3. Challenges and Limitations of Toxicogenomics

While toxicogenomics has the potential to improve the safety and effectiveness of drug therapy, some challenges and limitations need to be addressed. One of the main challenges is the need for large amount of high-quality data to identify genetic variations that are associated with drug response [46]. Additionally, there is a need for robust and validated methods for interpreting the results of pharmacogenomic testing, and for developing decision support tools for drug dosing and treatment selection. Another challenge is the need for standardization and regulation of pharmacogenomic testing along with proper education and training for healthcare providers to use the results of pharmacogenomic testing in clinical practice [47].

Furthermore, there are ethical considerations, such as privacy and discrimination, which need to be addressed when using toxicogenomics in personalized medicine [48]. Several nations have already adopted some regulations that are specifically geared toward genetic research or the gathering of DNA samples. For instance, the collection, maintenance, use, or provision of China's human genetic resources to foreign organizations is governed under China's Regulation of Human Genetic Resources. Similarly, in Brazil, the Resolution 340/2004 (NHC 2004) on genetic research and Resolution 2201/2001 on biorepository and biobank requirements have impact on how to conduct genetic research and how genetic specimens are stored, including the necessity of sharing any biobank samples with researchers in Brazil [49]. The regulatory restrictions and policies across the globe are different. As toxicogenomics is currently in a state where it is mainly performed for exploratory purposes, it may be unethically based on certain jurisdictions, and unlawful to return the patient genetic details to participants. Toxicogenomics is an emerging field that combines the study of genetics and drug metabolism to understand how an individual's genetic makeup can affect their response to a particular medication. Informed decision-making across the clinical development life cycle can be based on genetic analysis of clinical trial data, which may also result in significant clinical and business opportunities for patient classification and therapeutic value propositions [50]. However, there are several obstacles and restrictions to conduct genetic analysis during clinical development that include small sample size, lack of worldwide representation, and issues in validating results. Toxicogenomics has many potential applications in drug development and therapy, such as identifying genetic variations, optimizing drug dosing, and reducing the risk of adverse reactions [51]. However, some challenges and limitations need to be addressed, such as the need for large amount of high-quality data, the need for standardization and regulation of pharmacogenomic testing, and ethical considerations (published with permission from blog post) [52]. Additionally, reliable and consistent reproduction of results is a requirement for the successful application of toxicogenomics results in the regulatory setting regardless the approach being employed or the specific application planned. Thus, it is crucial to develop a trustworthy practice that is repeatable for in vitro TGx investigations. Given the quick development and evolution of genomic technologies, it is extremely difficult to ensure consistency and transferability in methods across the disciplines and between the laboratories and users.

4. Artificial intelligence in personalized medicine and toxicology

AI is a set of technologies that enable computers to simulate human intelligence and perform tasks that would typically require human intelligence, such as learning, reasoning, and decision-making [53]. AI analyzes large amount of data and makes predictions about treatment outcomes or toxicity. Healthcare is being transformed by AI and big data, especially for the analysis of complicated disorders. Human genomes and other biomarkers may easily be interpreted using machine learning and advanced computer techniques, which have significant applications in diagnosis and preventive care. For instance, patients' cardiovascular disorders can be diagnosed using artificial intelligence. Chest radiographs can be used to identify congestive heart failure using a neural network classifier. The study by Seah et al.[54] produce an intriguing result by using a generative adversarial network to directly see the traits that are used to create the prediction. It makes it possible to produce a visual output that is utilized to draw attention to pertinent aberrant characteristics in chest X-rays.

In personalized medicine, AI can be used to analyze patient data, such as genetic and molecular profiling data, to predict treatment outcomes and select the most appropriate treatment for individual patients. AI can also be used to monitor disease progression and determine the response to treatment; it also identifies the patients who may be at risk of adverse events. Preventive care for diseases with a higher chance of occurrence may be part of a patient's individualized treatment plan, such as increased cancer screening if the patient has BRCA 1 or BRCA 2 gene mutation. In addition, AI can anticipate a patient's response to various treatments using genetic data, biomarkers, and other physiological data. This can help patients avoid negative side effects preventing unnecessary expensive medicines. The most difficult issues in individualized care are being solved with the help of AI and precision medicine rendering a translational approach from the molecule to the bedside, particularly for those complex diseases in which gene-environment interactions have a role. Customized healthcare dogma (Fig. 5) could be a fantasy by nature but could advance with AI.

In toxicology, AI can predict the toxicity of chemicals and other agents based on their structure and properties [55]. This can help to identify potentially hazardous compounds and prioritize them for further testing. AI can also be used to analyze large amount of toxicology data, such as from animal studies, to identify patterns and predict toxicity in humans. In addition, the positive effects and properties of natural compounds as anti-cancer, anti-inflammatory or anti-viral/bacterial/fungal molecules can be tested by the standard in vitro or advanced cell models and effectively validated by AI tools [56, 57]. In order to be able to anticipate from datasets, AI algorithms use learning methodologies based on categorization or pattern recognition to (multi-dimensional) input data. For instance, in clinical medicine, this may entail using pathological specimen outcomes to forecast the diagnosis and staging of the pathological specimen that is obtained on a new patient. There are numerous AI algorithms available, which can be generally classified as either supervised or unsupervised. Support vector, random forest, neural network, and evolutionary algorithms are some of the techniques (EA) [58].

4.1. Applications of AI in personalized medicine and toxicology

AI has the potential to revolutionize personalized medicine by providing new ways to analyze patient data and make predictions about treatment outcomes. The application of AI in healthcare is a burgeoning field of development that could potentially impact healthcare provision. One of the earliest applications of precision medicine at scale is perhaps genome-informed prescribing. However, making real-time recommendations depends on creating machine learning algorithms to anticipate which patients would probably require a drug for certain genomic information. Genotyping individuals before that information is required is the key to customizing drugs and dosages. Similarly, AI-mediated analysis of hundreds of exomes, and distinct molecular subgroups of medulloblastoma have already been identified. This has made it easier to administer the appropriate medication, at the appropriate dosage, to the appropriate cohort of pediatric patients. Some examples of AI applications in personalized medicine include:

- Predictive modelling: AI enables patient data analysis, such as genetic and molecular profiling data, to predict treatment outcomes and select the most appropriate treatment for a patient. It can also predict the effectiveness of an existing or a new drug candidate, based on the complex OMICS data. For instance, AI has been proven

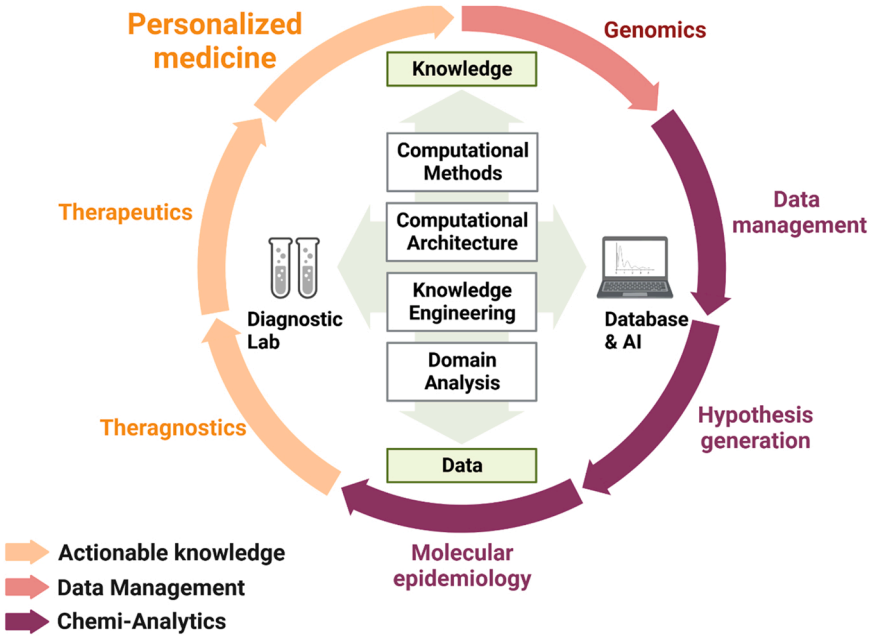

Fig. 5. The clinical applications of translational toxicogenomics in personalized decision-making. The flowchart of toxicogenomics data management involving epidemiology and theranostics in personalized decision-making shows the integration of genotyping, bioinformatics, and clinical decision-making to achieve personalized medicine.

effective in identifying new targets for cancer therapy and predicting drug efficacy [59].

- Disease progression monitoring: AI can monitor disease progression and determine response to the treatment, and identify patients who may be at risk of adverse events. The application of machine learning models in medical imaging on skin lesions enables automated classification of skin cancer [60].
- Drug development: AI examines large amount of data from drug development studies, such as pharmacokinetic and pharmacodynamics, to identify the patterns and predict the drug efficacy & toxicity.
- Clinical decision support: AI helps to develop decision supporting tools for drug dosing and treatment selection providing personalized treatment recommendations to healthcare providers. Clinical decision support has already been applied in several applications including paediatrics, traumatic brain injury risk classification [61], asthma assessment [62], antibiotic selection [63] etc.

AI also has the potential to revolutionize toxicology by providing new ways to analyze toxicology data and make predictions about toxicity [34]. Some examples of AI applications in toxicology include:

1. Toxicity prediction: AI can identify potentially hazardous compounds and prioritize them for further testing. For example, carcinogenicity testing is crucial for locating potential carcinogens while developing new drugs and evaluating the potential risks of environmental chemicals. In order to predict carcinogenicity for small compounds, Li et al. [64] recently create the DeepCarc model. A test set of 171 compounds is used to assess the DeepCarc model, which is constructed using a dataset of 692 chemicals.

- Data analysis: Toxicogenomics is a branch of toxicology that studies the harmful effects of chemicals or xenobiotics at the gene and/or protein levels in specific cells or tissues of an organism [18]. It does this by using genomic technologies (such as gene expression profiling, proteomics, metabolomics, and related approaches). In addition to acting as biomarkers for predictive toxicology, toxicogenomics has become a key technique in the identification of putative molecular pathways of toxicity at the gene, protein, or metabolite level in cells or tissues of organisms in response to exposure to environmental toxins. Molecular endpoints resulting from toxicogenomics data can be correlated with in vivo regulatory-relevant phenotypic toxicity or toxicokinetic endpoints (e.g., machine learning and PBPK models) [65,66]. In a recent study, scientists gather time-series toxicogenomic data from in vitro assays on the expression of a library of 38 key proteins (covering all recognized known DNA damage repair pathways) after exposure to a wide concentration range of 20 selected genotoxicity-positive and genotoxicity-negative chemicals [67]. This study shows that toxicogenomic data may be analyzed using machine learning techniques, connecting molecular level biomarker data to regulatory-relevant in vivo phenotypic and toxicity endpoints.
- Risk assessment: AI can examine large amounts of data from environmental and human studies, to identify patterns and predict the risk of exposure to chemicals and other agents [68]. In this scenario, Adverse outcome pathway analysis is a conceptual framework that represents the current understanding of the relationship between a direct molecular initiating event and an unfavorable result at a biological level of organization that is pertinent to risk assessment for human health.

4.2. Challenges and limitations of AI in personalized medicine and toxicology

While AI has the potential to revolutionize personalized medicine and toxicology [69], there are still several challenges and limitations; these include:

1. Data availability and quality: AI requires large amount of high-quality data fitting to translational toxicogenomics to train and validate algorithms as shown in Fig. 5. This can be a challenge in personalized medicine and toxicology, where data is often limited and of variable quality [70]. Machine learning methods are increasingly being used to analyze toxicological data, but there is disagreement on the appropriate algorithm for a specific dataset or type of data. Various algorithms have distinct needs in terms of the

quantity and kind of data (e.g. continuous vs categorical). Researchers must test multiple algorithms and evaluate their results to design the optimal model.

- Algorithm validation: AI algorithms need to be robust and well validated to ensure that they produce reliable results. This can be a challenge in personalized medicine and toxicology, where the complexity of the data and the variability of patient responses can make algorithm validation difficult [71]. For instance, insufficient coverage of pathways and chemicals in the applicability of domain of particular models is a common problem in carcinogen assessment using AI. A weight of evidence model-based on machine learning was created by combining integrating results from several models with complementary mechanisms like QSAR model, *in silico* toxicogenomic models and structural alert models [72].
- Interpretation of results: AI-driven analyses can be complex and difficult to interpret. This can be a challenge in personalized medicine and toxicology, where the results of AI-driven analyses need to be translated into actionable recommendations for healthcare providers and patients [73].
- Bias and discrimination: AI-driven approaches can be affected by bias and discrimination, which can lead to inaccurate or unfair results [74]. This is a concern in personalized medicine and toxicology, where AI-driven approaches can be used to make important decisions about patient treatment and exposure to chemicals.
- The use of machine learning models in toxicology is complicated by the fact that many people perceive artificial intelligence and machine learning algorithms as "black boxes" that lack mechanistical explanation. Knowledge-based machine learning techniques should be created to get over this restriction and provide interpretable predictions. Further, Traditional machine learning techniques have difficulty in identifying crucial information, making it challenging to anticipate the future events accurately. This data frequently involves a large number of substances with many fingerprint descriptors as more high-throughput data becomes accessible. The performance on model validation may be hampered by many machine learning models' tendency to overfit, however, these restrictions may be solved by more sophisticated deep neural network models.
- Transparency and interpretability: AI-driven approaches can be difficult to understand and interpret. This can be a challenge in personalized medicine and toxicology, where the results of AI-driven analyses need to be transparent and interpretable ensuring that they are trusted and accepted by healthcare providers and patients [75].

The reliance on preclinical and clinical studies may diminish as the data continue to grow and become more accurate [76]. The predictive power of the available AI techniques has significantly improved, although there is still considerable room for improvement given the complexity of toxicology. For instance, predictive carcinogenicity models are not accurate or reliable enough to entirely replace in vitro or in vivo research. The topic of artificial intelligence seems to have only recently come up in toxicology conversations (as of 2016); nevertheless, the data suggest that AI has been around since 2011, thus indicating the scope for better data translation between toxicology and AI [76].

4.3. AI tool applicable in toxicogenomics linking toxicology and personalized medicine

AI algorithms use learning methodologies based on categorization or pattern recognition to anticipate future datasets (multi-dimensional). For instance, in clinical medicine, this may entail using pathological specimen outcomes to forecast the diagnosis and staging of the pathological specimen that is obtained on a new patient. There are numerous AI algorithms available, which can be generally classified as either supervised or unsupervised. Support vector, random forest, neural network, and evolutionary algorithms are some of the techniques (EA). Recently, both neural network-based machine learning and EA techniques have been combined for applications that cannot be addressed by usually polynomial algorithms (Fig. 6). Some of the common AI-based algorithms that are currently used for applications in toxicogenomics and toxicology are listed below.

- Machine learning algorithms: These are a type of AI that can learn from data and make predictions without being explicitly programmed [77]. Machine learning algorithms enable toxicogenomics to identify genetic variations that are associated with drug response, and to develop decision-support tools for drug dosing and treatment selection.
- Natural Language Processing (NLP): This is a branch of AI that deals with the interaction between computers and humans using natural language [78]. NLP can be used to extract information from electronic health records, literature and other sources to aid in pharmacogenomic research.
- Predictive modelling: This is a type of machine learning that serves to make predictions about future events based on historical data. Predictive modelling helps toxicogenomics to identify the individuals who may be at increased risk of adverse reactions to a particular medication and predict treatment outcomes [79].
- Artificial Neural Networks (ANN): ANN is a type of machine learning algorithm that can predict and help in decisions making based on a large amount of data [80]. ANN supports toxicogenomics to identify genetic variations that are associated with drug response and develop decision-support tools for drug dosing and treatment selection.
- Deep learning: This is a subset of machine learning that uses neural networks with multiple layers to learn from data [77]. Deep learning can analyze large amounts of genetic and molecular profiling data, and make predictions about treatment outcomes and toxicity.
- Computer-aided drug design (CADD): It is an AI-based tool that predicts the properties of chemical compounds and optimizes drug design [81]. CADD further helps to identify potential drug candidates that have a favorable genetic profile and optimize drug dosing and treatment selection.
- Toxicity prediction models: These models use AI algorithms such as machine learning and deep learning to predict the toxicity of chemicals based on their structural and properties data [82].

4.4. Prediction models

A large amount of the toxicity data is evaluated using quantitative structure-activity relationships (QSARs) predictions for two to three thousand compounds per year [83]. Their utility is severely constrained due to their uncertainty. With the advent of the REACH system, which states that "No Data, No Market" for all chemicals, the EU and other nations that had previously been extremely passive in introducing QSARs, are now aggressively investing in the development and extension of the QSARs program. Additionally, institutional backing has been formed to demand that non-testing techniques, such as QSARs, be discovered first before performing a new toxicity test for REACH registration [83].

Quantitative Structure-Activity Relationship (QSAR) models: QSAR models use quantitative algorithms to predict the toxicity of chemicals based on their chemical structure and properties [84]. These models can be used to identify potentially hazardous compounds and prioritize them for further testing. Machine learning algorithms are viewed differently by certain people than by others. A structure-activity relationship is typically used in QSAR modelling to model a quantitative label prediction. Machine learning, on the other hand, refers to the use of a statistical method to generalize the data and produce predictions based on the model. Structure-activity relationships can be utilized to model the data in machine learning, which could lead to confusion between the two modelling approaches[85]. Additionally, it should be

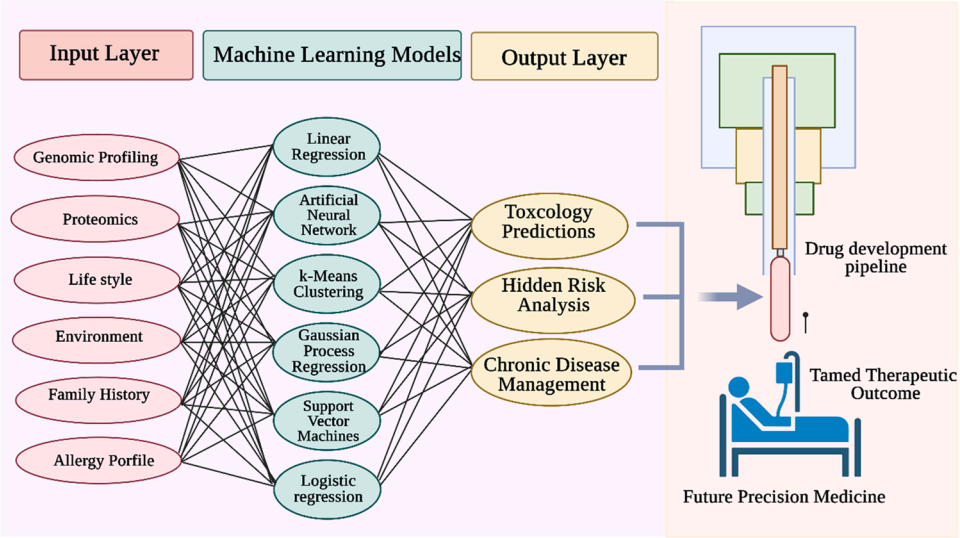

Fig. 6. Toxicogenomics pipeline involving machine learning algorithm and AI. The toxicogenomics pipeline starts with the collection of genomic data from patients, including DNA sequencing and genotyping. This data is then used to identify genetic variations associated with drug response. Machine learning algorithms are applied to the genomic data to create predictive models of drug response. These models can be used to predict how a patient would respond to a particular drug based on their genetic profile. The integration of AI in toxicogenomics can enhance the ability to identify novel drug-gene interactions and improve the accuracy of predictive models in precision medicine.

emphasized that machine learning allows for the modelling of data using features other than structure, therefore the structure is not mandatory. Similar to this, the compound's activity need not have the predicted label, and other labels are acceptable.

2. Adverse drug reaction prediction models: These models use AI algorithms to predict the likelihood of adverse drug reactions based on patient data such as genetic and demographic information [86]. These models assist in identifying patients who may be at risk of adverse reactions to a particular medication and selecting alternative treatments that may be safer for these patients [57].

3. Drug-drug interaction prediction models: These models use AI algorithms to predict the likelihood of drug-drug interactions based on patient data such as genetic and demographic information, and medication history [87]. These models can identify patients at risk of drug-drug interactions, and select alternative treatments that may be safer for these patients [88].

4. Risk assessment models: These models use AI algorithms to analyze large amount of data from environmental and human studies to identify patterns and predict the risk of exposure to chemicals and other agents [89].

5. Decision support systems: These are AI-based tools that can be used to provide personalized treatment recommendations to healthcare providers based on patient data such as genetic and demographic information, and medication history [90].

There are several free, open-source prediction software models available for use in toxicogenomics, linking toxicology and personalized medicine.Table 1.

It is important to keep an eye out for new and updated software tools that may become available since the field of AI and toxicogenomics is rapidly growing. Additionally, some of these tools may require a certain level of expertise to use them.

5. Current trends and future perspectives

The progress of toxicology research over the years has proven that scientific trends ebb and flow in the field of toxicology just like in other disciplines. While some dominant ideas like zebrafish models continue to pertain over years, new concepts like AO are not considered the game-changer they are expected to be. However, that does not seem to be the case, with ideas like the microbiome and personalized medicine occupying prominent positions [100]. The limitation posed by AI regarding data availability and translation continues to hold AI only as a preliminary tool rather than a highly reliable end point to toxicology studies.

In the future, toxicology is expected to become even more important in protecting human health and the environment [101]. There would be an increasing focus on using AI to predict the toxicity of chemicals and other agents, furthermore, it could well be used to analyze large amount of toxicology data. Additionally, there would be a growing emphasis on using toxicology data to inform policy decisions and protect vulnerable populations. Toxicogenomics plays a crucial role in connecting personalized medicine and toxicology by providing information on how an individual's unique genetic makeup can affect their response to treatment and exposure to chemicals. It can be used to optimize drug dosing and reduce the risk of adverse reactions in personalized medicine predicting the toxicity of chemicals in toxicology. In future, toxicogenomics is expected to play an important role in connecting these two fields, as more genetic and molecular profiling data becomes available and AI algorithms improve [102].

5.1. The impact of artificial intelligence on personalized medicine and toxicology

AI is having a significant impact on personalized medicine and toxicology by providing new ways to analyze patient data and make predictions about treatment outcomes or toxicity. AI can examine large quantity of data and make predictions about treatment outcomes, and toxicity, which can aid in decision-making and improve patient outcomes [103]. Additionally, AI can monitor disease progression and determine the response to treatment, and identify patients who may be at risk of adverse events. In future, AI is expected to improve the accuracy of predictions about treatment outcomes and toxicity aiding the development of new treatments and drugs.

Personalized medicine, toxicology, toxicogenomics, and AI are fields that are rapidly advancing and evolving. Personalized medicine and toxicology are becoming increasingly important in the era of precision medicine, and toxicogenomics plays a crucial role in connecting these two fields. AI is having a significant impact on personalized medicine and toxicology by providing new ways to analyze patient data and make predictions about treatment outcomes or toxicity [100,104]. In the future, these fields are expected to become even more important and continue to evolve as technology advances.

6. Outlook: the role of personalized medicine, toxicology, toxicogenomics and artificial intelligence in the era of precision medicine

Personalized medicine, toxicology, toxicogenomics, and AI are four

Table 1
List of prediction software for use in toxicogenomics and toxicology.

Tools	Features	Remarks	Reference
OpenTox	Multiple models for toxicity prediction and risk assessment. Including QSAR modelling, machine learning, and data visualization.	Open-source, Guarantees the portability of components by enforcing language-independent interfaces	[91]
Toxtree	Based on structural and properties data and applies decision tree approach i.e. statistical and knowledge base	Open-source, More interpretable and can guide molecule modification, suitable for non-specialised users	[92]
R/PharmacoGx	R package for toxicogenomics data analysis. It includes tools for data visualization, machine learning, and statistical analysis	Open-Source. Also identifies molecular features associated with drugs effects	[93]
OpenPKG	C+ + model for whole body physiology. Leverages data from physiochemical data and from in vivo studies to determine the time evolution of drug distribution and clearance on an organ-specific level	Open-source, compartmental framework for analyzing protein-drug binding and drug metabolism and degradation	[94]
SafetyPharma	A platform for drug safety analysis. It includes tools for data visualization, machine learning, and statistical analysis.	Commercial	[95]
ADRpred	Predicts adverse drug reactions. It uses machine learning algorithms to predict the likelihood of adverse reactions based on patient data. knowledge-based	Open-source, uses knowledge graph embedding to effectively encode drugs	[96]
ToxCast	Database of in vitro toxicity assays for use in predicting the toxicity of chemical mixtures	Research project. Focus on the molecular and cellular pathways that are targets of chemical interactions	[97]
Virtual ToxLab	predict the toxic potential (endocrine and metabolic disruption, some aspects of carcinogenicity and cardiotoxicity) of existing and hypothetical compounds (drugs, chemicals, natural products)	Simulates and quantifies their interactions towards a series of proteins suspected to trigger adverse effects using automated, flexible docking combined with multi-dimensional QSAR	[98]
Deductive estimate of risk from existing knowledge (DEREK)	Prediction based on chemical structure, and toxic functional groups. correlation between structure and biological activity i.e. Knowledge-based.	Commercial, Working towards integrating multiple prediction programs	[83]
DanishQSAR	A repository-based model with prediction related to physicochemical characteristics, acute toxicity, skin irritation and environmental toxicity	Limited to only 600000 chemicals and 200 QSAR models.	[83]
VegaHubQSAR	Built to meet REACH requirements and contains 40000 chemical data. Can predict mutagenicity, carcinogenicity, skin irritation, endocrine binding, developmental toxicity and physicochemical properties.	Possible batch prediction	[83]
PreADMET	Statistitical tool for carcinogenicity prediction models and genotoxicity prediction	Commercial, Limited by the data from mouse models and Ames test	[99]

fields that are becoming increasingly interconnected. Personalized medicine aims to optimize treatment outcomes by taking into account an individual's unique characteristics, such as genetics, lifestyle, and environment [105]. Toxicology informs the effects of chemicals and other agents on living organisms, and how these effects can be prevented or mitigated. Toxicogenomics informs the effect of an individual's genetic makeup to a particular medication.

- In personalized medicine, AI can forecast patient data, such as genetic and molecular profiling data, to predict treatment outcomes and select the most appropriate treatment for an individual patient. In toxicology, AI can envisage the toxicity of chemicals and other agents based on their structure and properties. Toxicogenomics plays an important role in connecting these two fields, by providing information on how an individual's unique characteristics can affect their response to treatment and exposure to chemicals.
- Another challenge in personalized nanomedicine during the COVID-19 pandemic is the difficulty in controlling virus transmission due to limited data [106,107], especially in the case of new variants with higher transmissibility [106]. This makes it hard to conduct clinical trials and test the safety and efficacy of personalized nanomedicine treatments on COVID-19 patients [28,46]. Additionally, the rapid spike of infection in some areas makes it hard to reach and treat patients who need personalized nanomedicine treatments. This can also lead to a shortage of medical resources, including equipment and staff, further complicating the implementation of personalized nanomedicine as a treatment option.
- It is anticipated that more models would be created to forecast toxicity, especially with new data sources and the reduction of computational costs brought on by technology advancements. However, efforts are certainly needed to address the bottlenecks of AI for predictive toxicology, in terms of the quantity and quality of the data. Although partnerships with pharmaceutical firms and publicly accessible web databases serve to some extent to reduce this problem, some gene or protein targets or even toxicological endpoints cannot be anticipated owing to the absence of necessary data [108]. Additionally, there are concerns about the potential for bias and discrimination in AI-driven approaches, and the need to ensure that these approaches are transparent and interpretable. Moreover, additional work is necessary to address the problem of unbalanced data in predictive toxicology, such as gathering and disseminating compounds' unfavorable experimental outcomes.
- Hepatotoxicity, carcinogenicity, cardiotoxicity, and mutagenicity are the main topics of recent predictive toxicology research, but other types of toxicity are generally understudied; a significant portion of human toxicity remains unknown. The community can get

closer to replacing in vivo toxicity testing with *in silico* approaches by learning more about all types of toxicity (and not just the major types of toxicity).

- Even as the need for additional data is evident, the industry's and regulators' acceptance of such *in silico* approaches is crucial for their broad usage. The regulations safeguard the consumers by guaranteeing that items have a stringent safety routine, enabling them to confidently utilize these products. It is necessary to develop protocols to check the accuracy and dependability of *in silico* technologies, which should also guarantee that reproducible outcomes can be attained. It must be shown that in vitro and *in silico* methodologies can produce risk evaluations with the same level of rigor as those made using conventional techniques and consistent mechanistic understanding.

7. Conclusions

We have studied personalized medicine, toxicology, toxicogenomics and AI usage in detail and found that these are becoming increasingly interconnected. They have the potential to revolutionize the way we understand and treat disease mitigating the adverse effects of chemicals, drugs and other agents. The existence of several comparative toxicogenomics is crucial in recovering, analyzing and comparing the novel information with recorded data. However, it is important to address the challenges and limitations that come with these fields to fully realize their potential. These challenges are found to be mainly the need for large amount of high-quality data, robust and validated methods, transparency and interpretability in the results. Additionally, it is important to consider ethical considerations such as privacy and discrimination when implementing these fields in clinical practice.

The era of precision medicine is rapidly approaching, and the integration of personalized medicine, toxicology, toxicogenomics and AI can play a vital role in achieving its goals. These fields can help to optimize treatment outcomes and reduce the risk of adverse effects, by taking into account an individual's unique characteristics such as genetics, lifestyle and environment. Furthermore, AI can help to analyze vast amounts of data and make predictions about treatment outcomes and toxicity. It is important to continue the research and development in these fields to improve patient outcomes and protect human health.

CRediT authorship contribution statement

A.V.S: Conceptualization, Formal analysis, Supervision, Writing – original draft, Writing – review & editing, and images, Funding acquisition. V.C: Conceptualization, Formal analysis Writing – original draft, Writing – review & editing, Validation. N.P.: Conceptualization, Formal analysis, Writing – original draft. P.L: Writing – review & editing and images. A.L: Conceptualization, Writing – review & editing. D.G: Formal analysis, Investigation, Validation. V.T: Formal Analysis, Writing – review & editing, Validation. K.S.P: Writing – review & editing & images. S.U: Writing – review & editing, Validation. S.P.D: Conceptualization, Writing – review & editing, Resources, Supervision, Funding acquisition.

Data Availability

No data was used for the research described in the article.

Acknowledgement

This publication was made possible partly by NPRP-11S-1219-170106 from the Qatar National Research Fund (a member of Qatar Foundation) and partly by IRGC-05-SI-18-360 from Medical Research Center, Hamad Medical Corporation, Doha, Qatar. The findings herein reflect the work and are solely the responsibility of the authors. The Open Access funding is provided by the Qatar National Library.

Conflict of interest

The authors declare no competing interest of interest at this point.

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