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Communication

Important Guide for Natural Compounds Inclusion in Precision Medicine

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Abstract

Precision medicine describes the definition of disease at a higher resolution by genomic and other technologies to enable more precise targeting of disease subgroups with new therapies. Preventative or therapeutic interventions can be developed with the knowledge of how a compound acts safely in the body to target receptors and produce the desirable effect. With the completion of the Human Genome Project in 2003 and the rapid increase in sequencing and bioinformatics tools, obtaining information about a person's genome is becoming more accessible. To make use of genetic information in precision or personalised medicine, it is important to examine the roles of natural remedies in the individualization of treatment - to use as the right drug, at the correct dose, for the right person, at the right time. Integrating biomarkers, especially within clinical workflows, plays a crucial role in implementing precision medicine. Though the horizon in precision medicine looks promising, one major issue resides in the precise mapping into clearly defined medical conditions associated with biomarker identification and precedence ranking. This communication is met to provide guidelines that could improve biomarker discovery and enhance the

participation and integration of novel natural compounds in the processes of implementing precision or personalized medicine.

Keywords
Precision medicine; natural compounds; gene; small peptide; anti-inflammation; antioxidant; biological pathways

1. Introduction

Plants and their derivative phytochemicals are an integral part of the immune system of living beings, including humans. About 80% of the world's population relies heavily on traditional medicine, including plant-based remedies, to address their primary health needs. Medicinal plants are commonly used to facilitate various disorders [1]. The usefulness of crude plant extracts as an alternative therapy to treat ailments is due to their affordability and widespread availability [1]. Natural products from plants have been the source of valuable drugs such as aspirin, reserpine, physostigmine, quinine, and ginseng. Hence, searching for natural products will continuously focus on medicinal plants [2]. In addition to the increasing numbers of people suffering from cancer, heart disease, diabetes, sepsis, and mental health issues such as depression and anxiety, modern medicine must address other problems, such as the growing antibiotic resistance by pathogenic bacteria and the lack of economic viable therapeutic methods for the treatment of neurological diseases [3]. Modern medicine can be overstretched unless rapid support is given through innovation in diagnosis, treatment discovery, and rapid responses to care. Hence, one angle that scientists should look into is the ability to standardize effective protocols for identifying, synthesizing, testing, and mapping the right bio remedies with druggable genetic targets. The advantage is that sourcing for such medicinal plants at a large scale has been easy by implementing plants as production factories to synthesize naturally synthesized bioactive molecules. Thus, it becomes a clear choice [1].

Precision and personalized medicine have been hot topics in medical health research. Precision medicine may be considered health care that is informed by and tailored to the individual patient [4]. Precision medicine can potentially transform how diseases are prevented, diagnosed, and treated. Precision medicine is already having an impact in some areas of medicine. One of the prime goals of understanding precision medicine is diagnostics and disease monitoring [4]. While diagnostics account for elucidating primary modalities toward understanding conditions, disease monitoring takes a step further and develops predictive methods for understanding possible symptoms without an apparent cause [5]. The combinations of global measurements that encode an understanding of the molecular trajectory of diseases and the knowledge of disease mechanisms provide new insights into precision medicine [6]. It has been recognized that the variability in individual's genetic variability has a role in how we respond to certain treatments. Since 90% of the variability of gene expression is a result of genetic variability in human populations [7], detecting and understanding the genetic variations and factors that impact human health and further the assessment of toxicities related to the genetic predisposition of populations to environmental challenges has been at the forefront of medical research for

decades [7]. A particular loci can influence observable phenotypes in humans, as more focus should now be on identifying and understanding the extent, distribution, and sources of gene variability in humans. This article outlined important guidelines for selecting biomarkers relevant to natural compounds and weighting the relevance to precision medicine. This approach might be very useful in administering combinational therapy tailored to individual needs and genetic variability.

2. Guide 1: Prioritising the Biomarkers of Interest

The most important step in utilizing findings from various studies on a choice of natural medicine is to first define the relevant biological pathways that are perturbed by the disorders and identify disease-correlated biomarkers or modifiers. For example, inflammation, oxidative stress, apoptosis, or inhibition of angiogenesis are some of the commonly involved pathologies in various diseases [8]. These biological functions have numerous biomarkers that can be refined for studies. To date, there are very few curated biomarker databases. The MarkerDB (https://markerdb.ca/) is a freely available electronic database that consolidates information on all known clinical and pre-clinical biomarkers into a single resource. The MarkerDB version 2 contains 218 protein biomarkers, 1,664 chemical biomarkers, 154 karyotype biomarkers, and 32,447 genetic markers. These are categorized into 25,760 diagnostic biomarkers, 13 prognostic biomarkers, 635 monitoring biomarkers, 45 safety biomarkers, 25 response biomarkers, and 12,674 risk biomarkers. Collectively, these markers can be used to detect, monitor, or predict 992 specific human conditions, which are grouped into 22 broad condition categories. Similarly, the Exposome-Explorer (http://exposome-explorer.iarc.fr) is the first database dedicated to biomarkers of exposure to environmental risk factors for diseases.

2.1 Scenario 1

The MarkerDB version 2 was filtered for genetic biomarkers in chromosome 17. Chromosome 17 is one of the most frequently mutated chromosomes in humans. It spans about 83 million DNA building blocks (base pairs) and represents between 2.5 and 3 percent of the total DNA in cells. Chromosome 17 likely contains 1,100 to 1,200 genes that provide instructions for making proteins. These proteins perform a variety of different roles in the body. The filtering criteria include Charm 17, human, clinical, or investigational, and all marker types.

2.2 Result

The database outputs a TSV file with a total number of 1107 markers of different types, e.g., single nucleotide mutations and deletions. When filtered by condition e.g. Alzheimer's disease, there are many clinical biomarkers and some investigational biomarkers. By clicking on each identification number, important metrics for each biomarker were assessed. The *SLC24A4* chr17:63460787 variant (rs138190086 (MDB00595443) is pathogenic, investigational, identified in the GWAS database, and associated with Alzheimer's disease. The logistic regression and AUC values for the sensitivity and specificity were also displayed.

One of the advantages of using a curated biomarker database for selecting a specific biomaker of interest, it saves time and prevents lengthy research since the database includes detailed

information on the nature of biomarkers, populations in which biomarkers have been measured, biospecimens analysed, and analytical methods used to measure biomarkers, concentrations in biospecimens, correlations with other types of exposure measures, and reproducibility over time. Hence, by accessing some of this information, researchers only need to compare the performance and field of application of various biomarkers and to identify the specific biomarkers or panels of biomarkers that are most useful for the natural compounds or bioactive compounds of interest. To achieve this feat, using an integrative tool based on a machine learning predictive model to prune and select best-fit biomarkers will be very paramount. The recent machine learning models have been, e.g., support vector machine, random forest, lasso linear regression, logistic regression, decision tree, and XGBoost for multidimensional data processing to predict biomarkers identified by top features are proving to be very useful in understanding the etiologies of metabolic disorders [9]. Biomarkers and features can be represented in mean ± standard deviation, while categorical variables can be expressed as absolute and percentage frequencies [9]. The Python 3.7 software package and sci-kit-learn toolkit have handy tools for processing and training datasets for each model. Researchers must also use metrics including accuracy, AUC, recall, and precision to evaluate the performance of the machine learning models. When performing the accuracy test, it is essential, therefore, to have a solid predictive ability, such as the AUC value being >0.8. The simplest way to find out is to run the package Lazypredict (https://github.com/shankarpandala/lazypredict). The tool takes input files, applies supervised models, and helps to understand which models work better without parameter tuning. There are enormous advantages in the application of this step, in the sense that it can accommodate the integration of different biomarkers, e.g., genetic, protein-based, safety, diagnostic, and so on. Besides, different classifications, such as exposure, biospecimen type, analytical methods used, and the nature of the cohort, can be adjusted for and modeled. With the advancement in machine learning, the contributions will be largely significant, and the impact on research cost and health delivery will be drastically improved. Nevertheless, the process is not error-free but promising. Also, it will require expertise to accomplish it. Many researchers are seeing this approach's benefits in accuracy, research meticulousness, and scaling. Nonetheless, the reproducibility remains a debate. Biomarkers offer a way of integrating molecular profile data with knowledge of changes between states, providing information that can directly assist in understanding the biological system's underlying changes. Such information is not always obvious; a biomarker can be used to identify a particular change in a biological state, and the molecular profile data can then be analyzed to discover the cause of the change. This scenario can also be applied to predict future outcomes, such as monitoring disease progression or treatment effects. In an even more complex setting, the data from molecular profile studies may be used to identify changes that lead to successful or adverse outcomes. In these cases, the biomarker can be used to translate the data into something more useful for clinical or therapeutic application.

3. Guide 2: Validating and Targeting the Mechanism of Actions

Figure 1 highlights certain steps that should be incorporated to validate the selected biomarkers of interest. This step should not be the usual procedure taken to study the mechanism of action of internal or external biological molecules in the body; rather, it should be a deliberate effort to prune and optimize biomarkers that have been known and established. Essentially, it is a

step to be taken to be more direct as regards the disease being modeled and the targeted natural compound to introduce. Pruning on this occasion entails adjusting the type(s) of the model used to identify the biomarker of interest. For instance, in a previous study where we reported the toxicity of monosodium glutamate and how it perturbed some vital organs, including liver enzymes, which in turn could lead to alterations in mental behavior [10], it is very crucial to know that the quantity ingested by the mice to alter the liver enzymes may differ in humans. Nonetheless, the dosage was standardized to be within the range of 0.9-1.5 g in humans to replicate similar effects. The validation of the biomarker step is a very important aspect of precision medicine that only a few people adhere to. It is very likely that by mathematically equating the test model (mice) to the replication model (human) and adjusting for all parameters, more precise delivery of medicine against ailment will be rapid and effective. When testing a natural compound or isolate, we should take caution before extrapolating the dosage in animal models to humans. Researchers may like to use other validation methods like experimental assays and computational and statistical methods, e.g., meta-analysis, to validate the selected biomarkers from the curated databases that have been modeled for the disease of interest. Therefore. The correlations of biomarkers with exposures matter a lot. The Exposome-Explorer (http://exposome-explorer.iarc.fr) tool is essential in this case. Under the correlation menu (http://exposome-explorer.iarc.fr/correlations), the CSV file can be filtered for population, intake, biospecimen, and, most significantly, the correlation value/p-value used in finding the plausible correlation and likelihood of association. With the advancement in developing meta-analysis tools by various experts, researchers could access biomarkers with robust statistical correlations in multiple disease types and specific cellular functions.

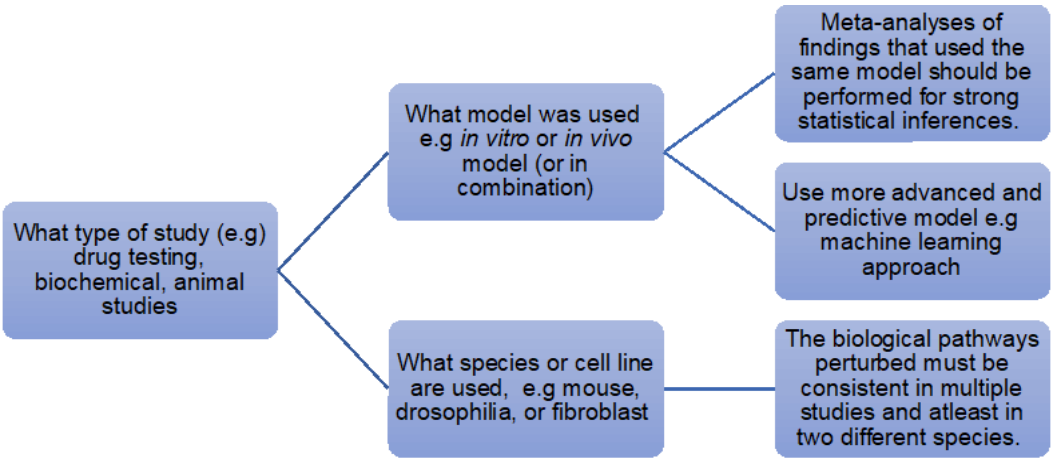

Figure 1 The descriptive guide towards utilising findings from various studies to select natural compounds of potential candidates for precision medicine.

Regarding targeting the mechanism of action, perhaps numerous studies have established many biological pure compounds that have anti-inflammatory, antioxidant, antipyretic, antidiabetic, anti-stress, immunologic, and pain relief. Inflammation is a condition characterized by swelling, pain, and loss of function caused mainly by the infiltration of inflammatory cells. They are major culprits in minor and major diseases. Reactive oxygen species (ROS) are involved in inflammation. They are essential to drive the onset and the progress of inflammation. ROS exert their actions via the activation of NFkB, which also involves cytokines. MDA is the hallmark of lipid

peroxidation in inflammation, while nitric oxide (NO) activation is the primary culprit in vascular tissue damage [8]. Physiologically, harmful effects of ROS can be suppressed by endogenous antioxidant chemicals such as superoxide dismutase (SOD), catalase, and glutathione synthesized by cells. Still, in severe conditions, endogenous antioxidants can be overpowered, resulting in progressive tissue damage. They proliferate in the early phase, causing neurogenic pain, while the late phase induces inflammation. Several natural compounds derived from plants have been described to have anti-inflammatory and antioxidant properties [2, 11-18]. Some other compounds include Curcumin, Resveratrol, and Quercetin, which are currently promising in precision medicine [1]. In many cases, these natural products and their derivatives have proven to be more effective than synthetic analogues. This has led to a need for further natural product research and has driven the development of enabling tools and technologies that will allow for broader chemical space exploration and rapid, efficient compound and material synthesis. It is somewhat surprising to find the difficulty that practitioners have faced in the study and synthesis of naturally occurring compounds. For such molecule-rich sources of complex materials, nature has evolved to produce an astonishing diversity of structures. It is natural product chemistry and the targeting of biologically relevant compounds that chemists and the chemical industry strive for, and yet it is only now becoming a realistic prospect. For example, through natural products that have been validated by their mechanisms of action on different therapeutic biomarkers, active small peptides can be synthesized for more precise usage. Small peptides (SPs), ranging from 5 to 100 amino acids, play integral roles in plants due to their diverse functions.

Indeed, as proposed by many experts, the validation processes should also include compound/ligand pharmacokinetic properties analysis. In this step, by using software like software DataWarrior V5.5.0 and SwissADME (http://www.swisstargetprediction.ch/), the pharmacokinetic study of the compound to be validated against the selected biomarkers can be justified using the Lipinski's rules of drug discovery that postulated that the compound with pharmacokinetic properties i.e., compounds that encompasses oral bioavailability (OB ≥ 30), molecular weight (MW < 500 Da), drug Likeness (DL ≥ 0.18), hydrogen bond donors (H donor < 5), octanl water coefficient (P < 5) and hydrogen bond acceptors (H acceptor < 10) are ideal for study [19].

3.1 Scenario 2

Previous studies showed that Jobelyn®, a sorghum-based compound, has anti-inflammatory, anti-stress, and anti-oxidant properties [12, 13]. One of the most abundant active compounds in Jobelyn® is apigeninidin [15]. To validate the compound against the mechanisms of action, i.e., anti-inflammatory, a PubChem query of the small peptide apigeninidin was carried out, followed by the pharmacokinetic properties of SwissADME.

3.2 Result

Apigeninidin is curated and cataloged in PubChem as a sorghum bicolor phytoalexin with the structure given in the first instance (Figure 2). The purified peptide for apigeninidin is $_{1}$GYQDOAKHUGURPD-UHFFFAOYSA-N$_{25}$. When the SMILES notation of apigeninidin (C1=CC(=CC=C1C2=[O+]C3=CC(=CC(=C3C=C2)O)O)O.[Cl-]) was analyzed in SwissADME, the data shows that the compound is water soluble 7.37e-02 mg/ml; 2.54e-04 mol/l and can be well

absorbed in the gastrointestinal tract with high bio-availability. The data supported its drug likeliness and compliance with Lipinski's rules. Hence, this compound can be purified and modified for targeted precision medicine for higher accuracy.

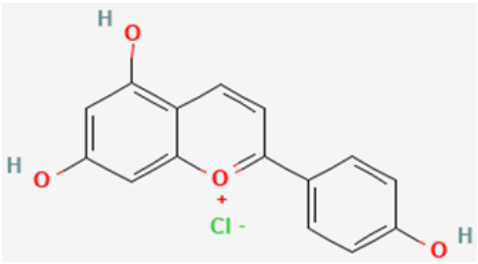

Figure 2 The chemical structure of apigeninidin with a molecular weight of 290.70 g/mol.

4. Guide 3: Integrating the Prioritised Biomarkers to Achieve Precision Medicine

In modern medicine, genomics and precision medicine are inseparable. Genomics plays an emerging role in clinical and public health research. Applying genomic tools in practice and using human genomic information have aided the prevention and control of various diseases. One of the emerging applications of genomics to precision medicine includes genetic predisposition to adverse drug effects (pharmacogenomics). The standard practices for defining disease at a higher resolution by genomic and other technologies to enable more precise targeting of disease subgroups with new therapies entail integration. The importance of biomarkers and their application has significantly increased with the development of "-omics" technologies. Researchers in the life sciences can collect an incredible amount of information from a sample with these technologies. The efficiency with which this information can be used will depend on the knowledge of the changes in the biological system being studied. In this regard, it is vital to target the specific type of genetic variants with predictable impact on gene regulations and functions (Figure 3).

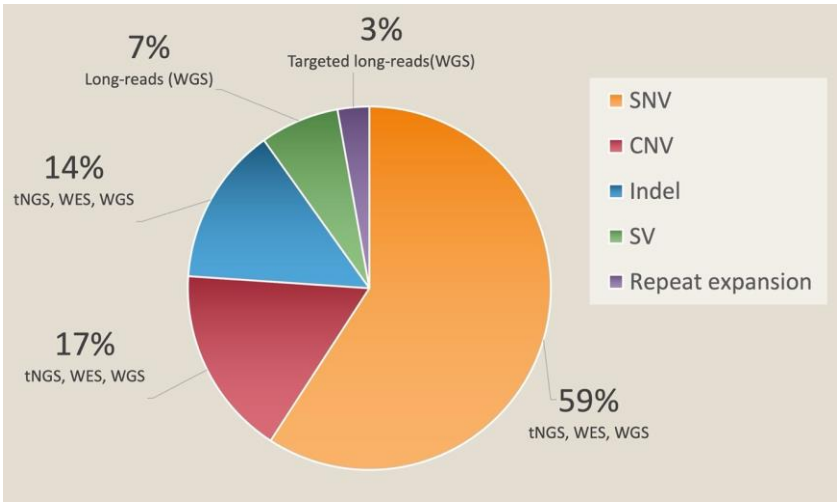

Figure 3 Sequencing methods most suitable for identifying the most common genetic biomarkers. Whole genome sequencing (WGS), Whole exome sequencing (WES), and Targeted next-generation sequencing (NGS).

Identifying actionable genetic variants can be challenging, especially when dealing with complex diseases. The screening approach will require multifaceted steps; nonetheless, conventional databases like OMIM, ClinVar, and, more recently, DisGeNET enable geneticists to have a robust knowledge of actionable genetic variants and phenotypes. It is noteworthy to have a custom database for project-specific goals, like the (https://diseases.jensenlab.org). Table 1 shows some of the publicly available tools that can be used to implement precision medicine.

Table 1 Various tools for identifying and curating genetic biomarkers in precision medicine.

Disease and phenotype classification databases and ontologies	
Name	**URL**
DAR	https://dar.biocomp.unibo.it
Disease Ontology	https://disease-ontology.org/
HPO	https://hpo.jax.org/app/
ICD	https://icd.who.int/en
MeSH	https://www.nlm.nih.gov/mesh/meshhome.html
MONDO	https://mondo.monarchinitiative.org/
OMIM	https://www.omim.org/
ORDO	https://www.orphadata.com/ordo/
Orphanet	https://www.orpha.net
Reactome	https://reactome.org
SNOMED	https://www.snomed.org/
UMLS	https://www.nlm.nih.gov/research/umls/index.html
Gene and protein network databases	
Name	**URL**
BioGRID	https://thebiogrid.org/
DIP	https://dip.doe-mbi.ucla.edu/
eDGAR	http://edgar.biocomp.unibo.it/
HIPPIE	http://cbdm-01.zdv.uni-mainz.de/~mschaefer/hippie/
IID	http://iid.ophid.utoronto.ca/
IntAct	https://www.ebi.ac.uk/intact/
Kegg	http://www.kegg.jp/
MatrixDB	http://matrixdb.univ-lyon1.fr/
mentha	https://mentha.uniroma2.it/
MINT	https://mint.bio.uniroma2.it/
OmniPath	http://omnipathdb.org/
ProfPPIdb	https://rostlab.org/services/ppipair
Signor	http://signor.uniroma2.it/
STRING	https://string-db.org/
WikiPathways	https://www.wikipathways.org/
Databases of variants	
Name	**URL**
ClinGen	https://clinicalgenome.org/

Clinvar	https://www.ncbi.nlm.nih.gov/clinvar/
dbNSFP	http://database.liulab.science/dbNSFP
dbSNP	https://www.ncbi.nlm.nih.gov/snp/
dbVar	https://www.ncbi.nlm.nih.gov/dbvar/
DisGeNET	http://www.disgenet.org/
EGA	https://ega-archive.org/
Ensembl Variation	https://www.ensembl.org/info/genome/variation
EVA	https://www.ebi.ac.uk/eva/
ExAC	https://exac.broadinstitute.org/
gnomAD	https://gnomad.broadinstitute.org/
GWAScatalog	https://www.ebi.ac.uk/gwas/
HGMD	http://www.hgmd.org
IGSR	https://www.internationalgenome.org/data-portal/
LOVD	https://www.lovd.nl/3.0/home
UK10K	https://www.uk10k.org/
UniProt/Humsavar	https://www.uniprot.org/help/humsavar_change
Varsome	https://varsome.com/

Genetic biomarkers are a measure or indicator of a biological state or condition. A popular theme in precision medicine is classifying patients into subgroups to determine an optimal treatment. Some biomarkers (phenotypic, biochemical, and genetic) can be studied in particular disease ontologies to prioritize targets [20-23]. The cellular processes, such as the program of cell death, the progression of a disease, or the effects of treatment, can all be measured by the presence and concentration of a biomarker [8]. When dealing with complex and multi-disorders, multiple biomarkers may be involved; hence, mapping the biomarkers to the affected organs can drastically improve the detection, diagnostic, and treatment options and predict an individual's predisposition to disease [24]. The sub-classification can be based on diverse data types, including genetic markers, gene expression levels, proteomic/metabolomic profiles, or a combination. Perhaps genetic biomarkers are most relevant to personalized medicine. Various diseases have been studied for deleterious genetic markers that can be targeted for treatments. For example, Parkinson's disease, hearing loss, and other rare disorders are attractive to this paper. Genetic biomarkers identified in previous studies in some patients are relevant to implementing precision or personalised medicine [25-29]. Nonetheless, pharmacogenomics biomarkers are still very difficult to underpin among many deleterious variants that can be identified in most pharmacogenes [30]. To accelerate the detection of pharmacogenomics biomarkers, collecting diverse biospecimens for genetic study should be paramount to identify strongly associated variants. If a successful novel candidate emanating from a medicinal plant is recognized and has been proven to have a significant correlation with the biomarkers of precision medicine, such a candidate should be documented and reported widely. As such, the plant can be widely cultivated and utilized since medicinal plants, mainly when grown under controlled conditions of plant tissue culture in bioreactors or using hydroponic and aeroponic systems, provide an excellent opportunity for raising large amounts of healthy plant material that can be used as a renewable source of bioactive compounds. Given these observations, Figure 4 recaps the steps that can be taken to further strengthen the actualization of precision medicine beyond molecular diagnostics

by utilizing one or more biomarkers for the specific diagnosis of a particular disease and screening multiple drug candidates that can have genetic and protein effects. Genetic mutations in diseases with a clear Mendelian inheritance pattern can be easily mapped genetically, leading to the development of a test for carrier detection and disease identification. The biomarkers involved, which include not only genomics but also proteomics, pharmacogenomics, metabolomics, and even lifestyle, can then be used to precisely stratify a patient's risk of disease, guide the choice of treatment, and then monitor that patient's response, or lack thereof, to that treatment. In an extended approach, it has been described previously to achieve precision medicine. There is a need for robust facilities like biobanking, genotype-phenotype tools, machine learning approaches, and artificial intelligence to drive the implementation [30, 31].

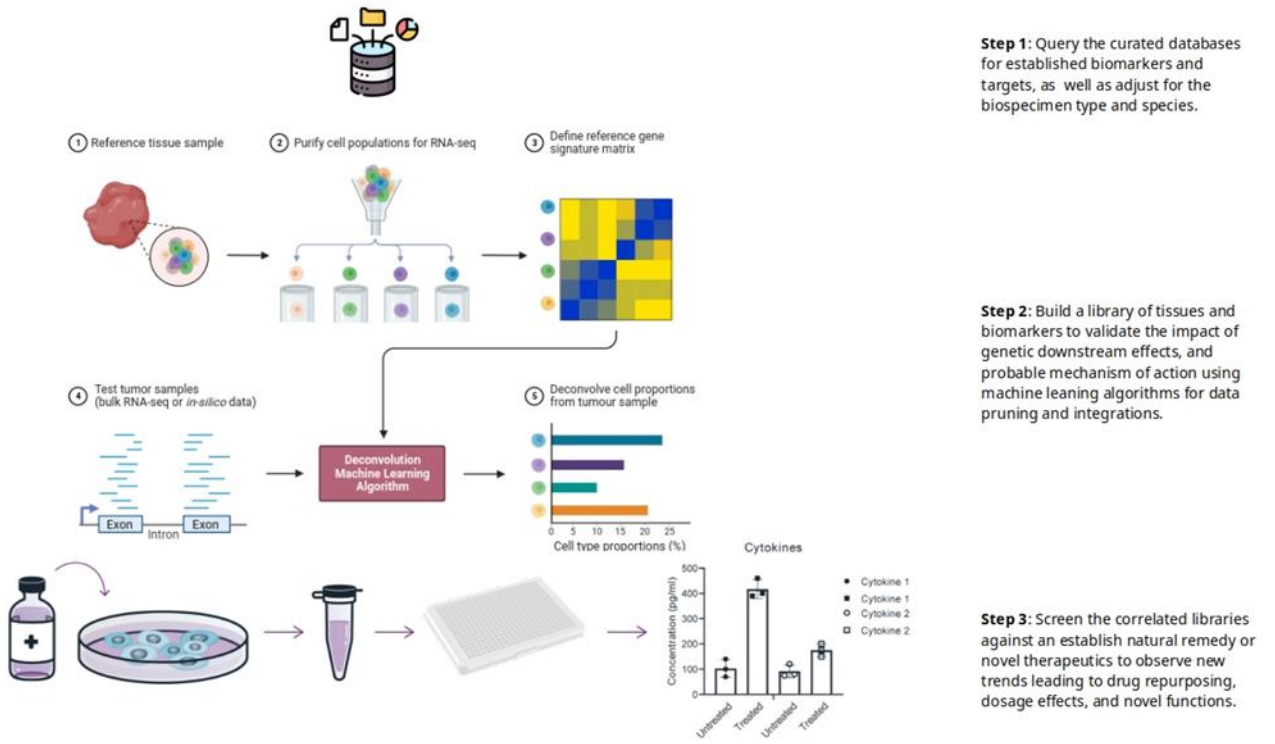

Figure 4 Graphical overview of the highlighted guidelines.

5. Conclusion

Given that broader clinical and biological understanding is often hindered by complex and multifaceted data sets from various technologies (e.g., high-dimensional genetic data with a small sample size or multi-level data structured by a hierarchy), the current rapid evolution of biomedical data presents excellent opportunities for the statistical community in terms of methodology development and collaboration with biomedical scientists. However, working with patient data presents unique challenges, and there is danger in applying methods designed for gene expression to proteomic data or methods developed in a non-clinical context to data that is heavily informed by clinical factors. Thus, statistical data analysis in precision medicine is required to ensure optimal practice. In this regard, statistical and machine learning methods are central in providing class discovery and prediction tools. These tools can be used to determine which variables or combinations of variables define the subgroups and to develop rules for assigning

future patients to the optimal treatment. An important goal is to provide an interpretable model to guide physicians in making treatment decisions. This will bring together the fields of statistical methodology, biomedical science, and clinical decision-making and hopefully lead to improvements in patient outcomes. This review attempts to describe the field's current state, identify challenges, and suggest areas for future research.

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Author Contributions

OGO conceptualised the idea and gained access to appropriate training and supports needed to write this article.

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Competing Interests

There is no conflict of interest.

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