Pharmacogenomics

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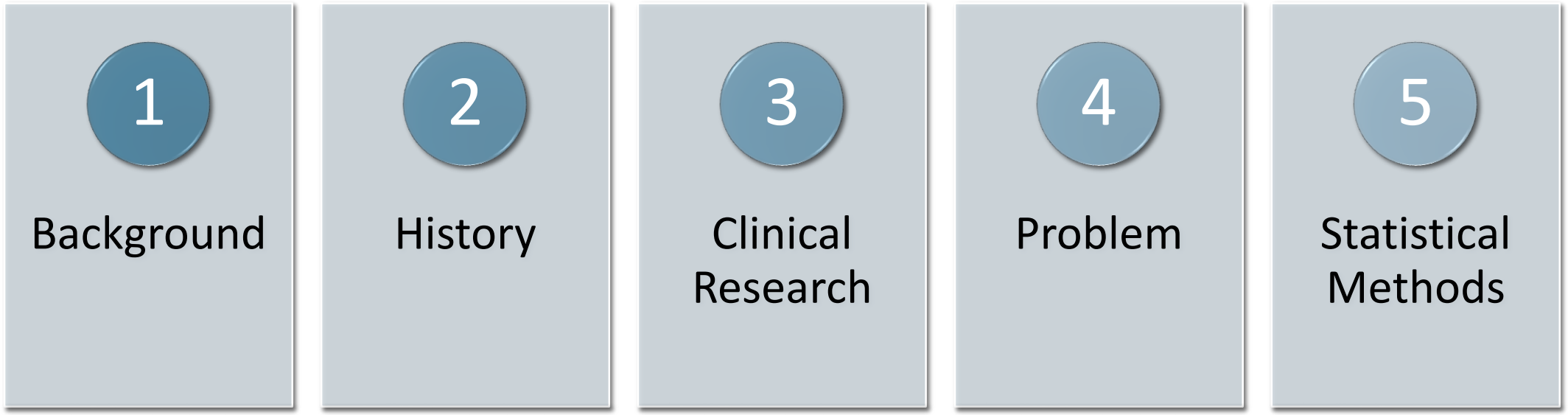
Overview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What is Pharmacogenomics?

Pharmacogenomics is an emerging field that combines pharmacology with genomics to elucidate how genetic variations influence responses to drug therapy.

This area of study is aware that no two patients are alike.

History

510BC

Pythagoras observed people suffering from potentially fatal hemolytic anemia by consuming fava beans whereas others did not. Result of a deficiency in glucose-6-phosphate dehydrogenase.

1906

Archibald Garrod was the first to propose that genetic variants might account for varying drug responses.

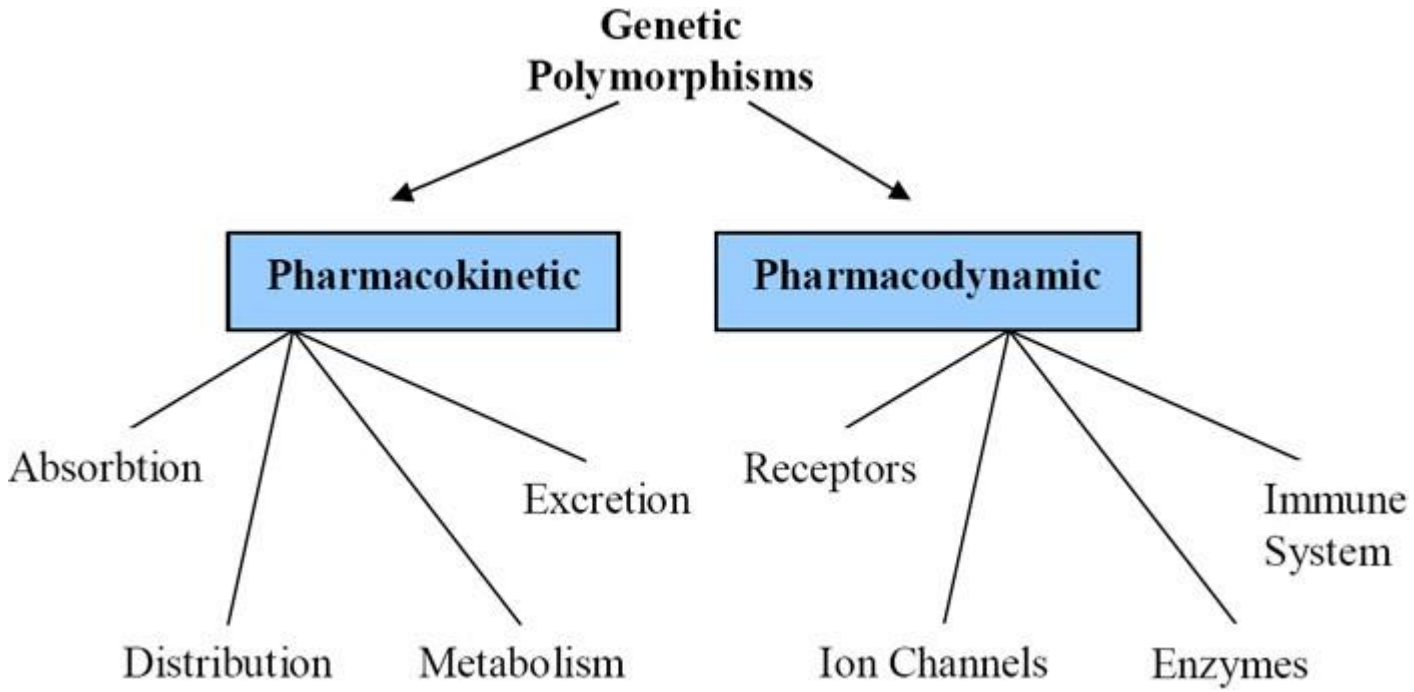
1959

Friedrich Vogel first coined the term “pharmacogenomics”.

2005

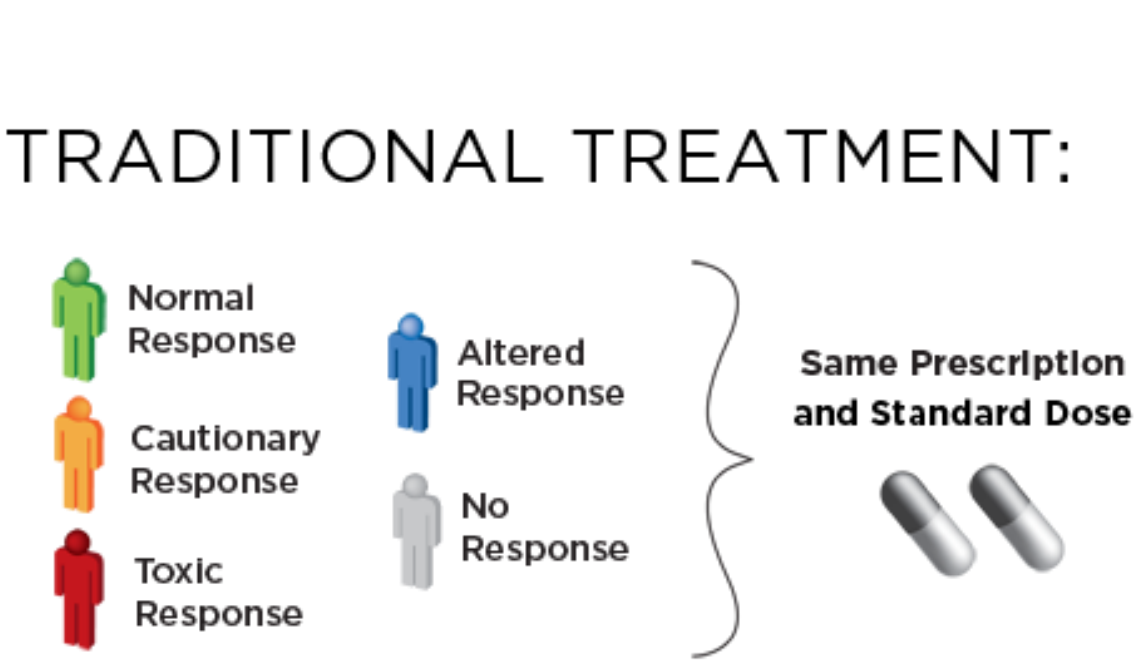
FDA approval of a pharmacogenetic test for the Cytochrome P450 alleles.

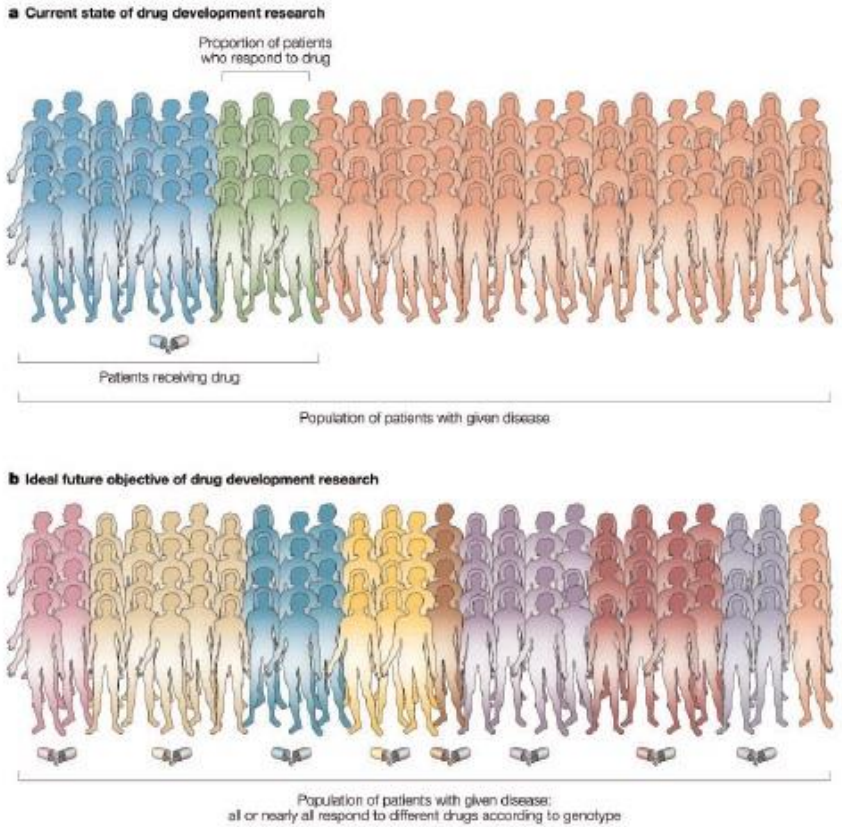
Pharmacogenomics: Searching for Biomarkers in Drug Action Studies



Personalized Treatment

Drugs are designed for a "one size fits all" approach.





Clinical Research

At present, regular drug trials assume that groups of research participants have little/no inter-individual variability.

Benefit from pharmacogenomic study due to the ability of pharmaceutical companies to target subgroups with specific genetic profiles.

Reduces chances of adverse effects. -> Lessen participant harm.

Saves resources.

Clinical Research

Gencaro was studied for the treatment of cardiovascular diseases.

However, development was canceled after competing drug companies won FDA approval first.

Recently, Gencaro has been of interest to researchers after it was found to benefit patients with a specific genetic variant.

Pharmacogenomics has the potential to revive drugs that did not make it to market.

Pharmacogenomic Clinical Trials

Different approach with pharmacogenomic drug trials:

- Assume that in participant groups variability is inherent.
- Change the way in which clinical trials are designed and statistically analyzed.

Pharmacogenomic Clinical Trials - Design

Currently, pharmacogenomic studies are designed under two main ideas.

1. Identify new genetic drug targets associated with various diseases or specific genetic polymorphisms that are associated with the responsiveness to particular drugs.
2. Look at SNPs to analyze drug response phenotypes.

Pharmacogenomic Clinical Trials – Issues

Ethical issues involve privacy, confidentiality, adequate informed consent, and storage of genetic samples.

The decision of a willing participant to enter a study might label themselves as ill - > create a bias towards a drug response.

The lack of standard terms interferes with the exchange of information between laboratories using electronic health records.

Example: “low function,” “low activity,” “null allele,” “no activity,” or “undetectable activity”

Pharmacogenomic Clinical Trials

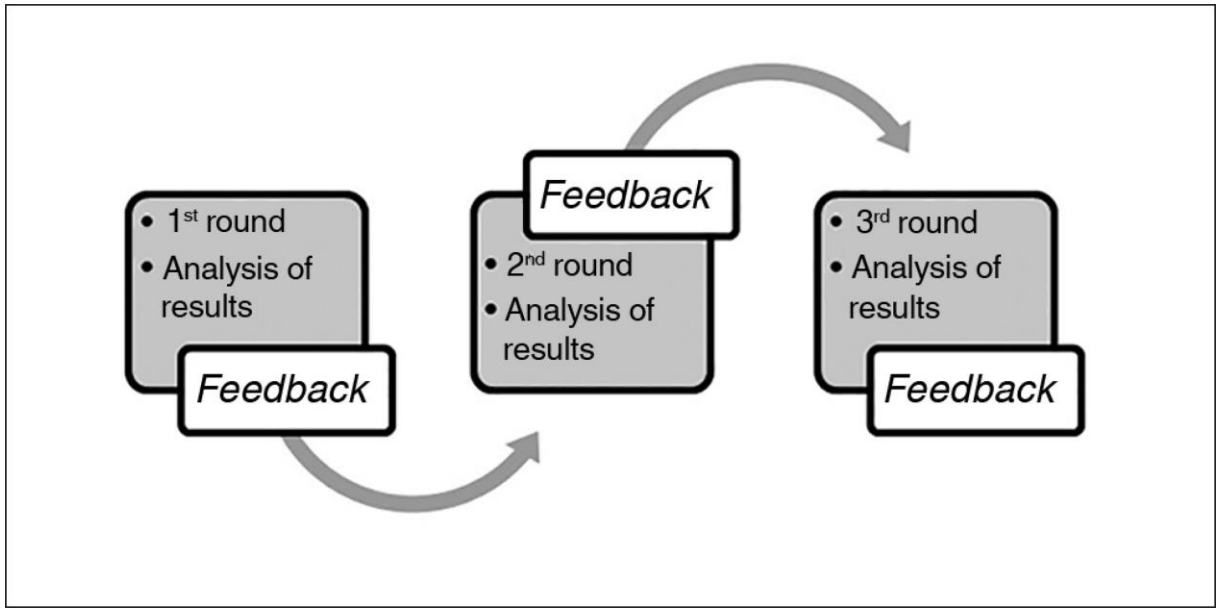
In 2009 The Clinical Pharmacogenetics Implementation Consortium (CPIC) was formed.

Establish clinical guidelines for the standardization of laboratory test results for specific drugs.

Used the Delphi model to identify terms that could be used consistently by developing a consensus amongst experts.

Pharmacogenomic Clinical Trials – Delphi Model Approach to Standardize Data

Series of surveys that relies on a panel of experts.



A full report is provided to the participants, presenting the consensuses achieved and the recommendations the group are produced.

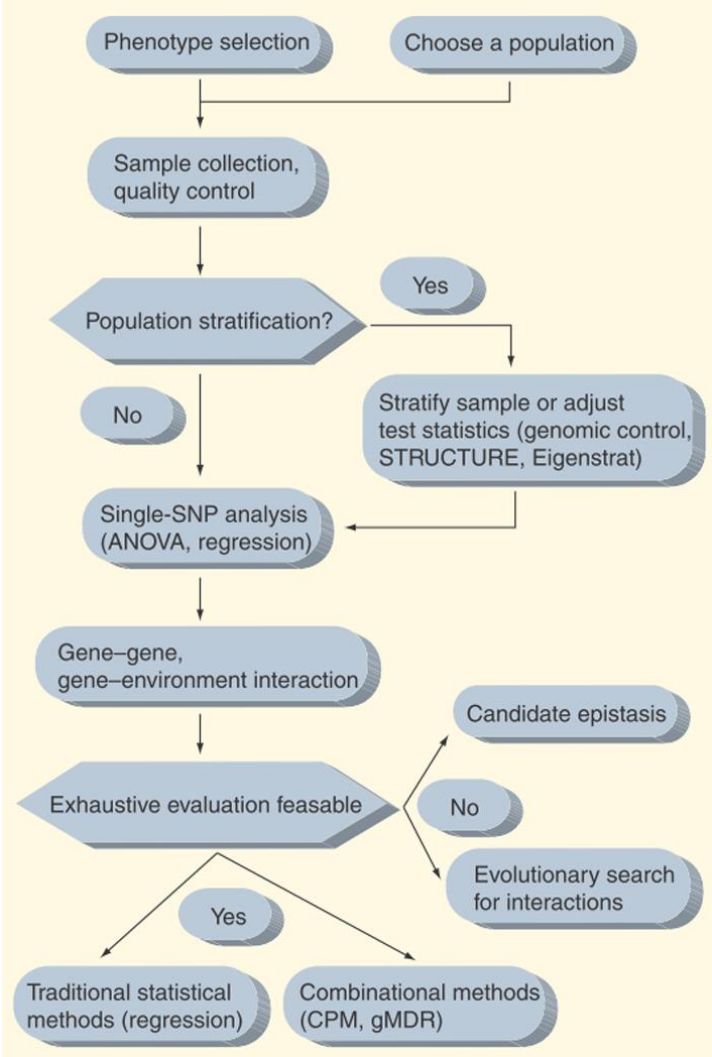
Pharmacogenomics – GWAS

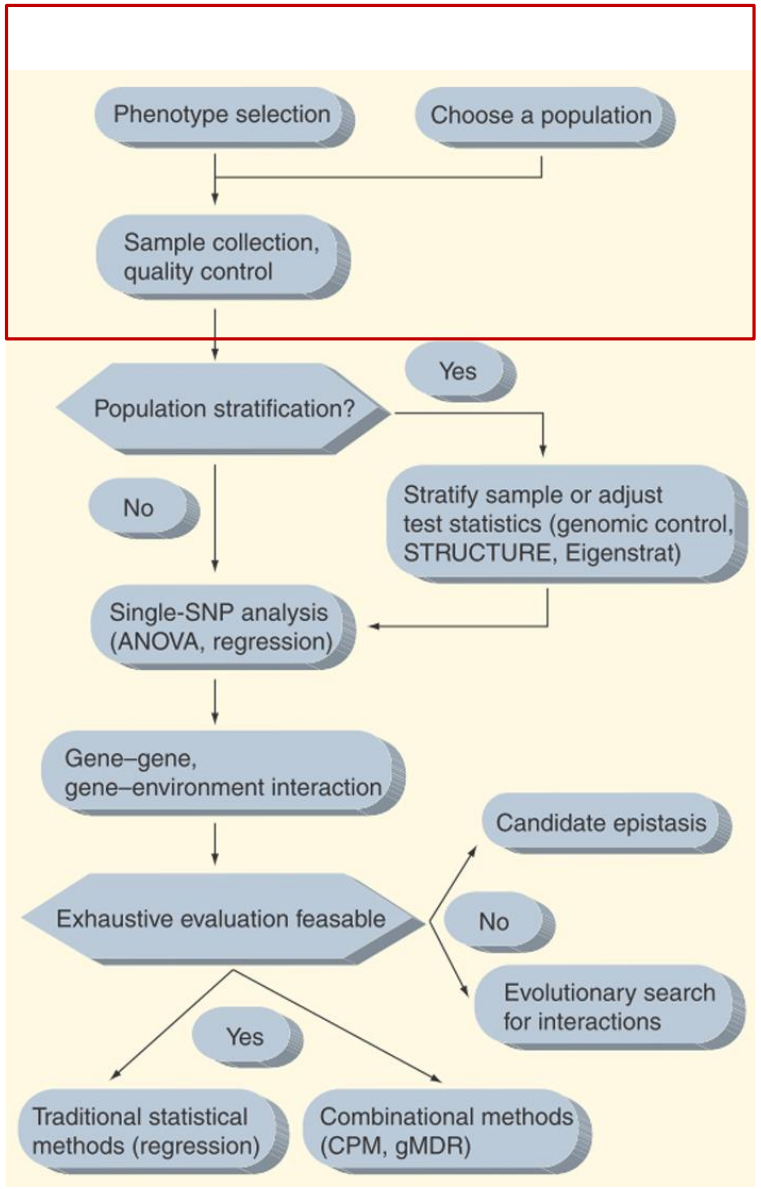
Most commonly applied modern genomic tool for analysis.

GWAS has already been used in many pharmacogenomic studies to identify common variants that influence adverse drug reactions, drug dosing and treatment efficacy.

Drawback -> Insufficient because they do not represent some of the known rare variants.

Solution -> NGS tools to examine rare variants missed in GWAS.


Phenotype selection
Choose a population
Sample collection, quality control
Population stratification?
Yes
No
Stratify sample or adjust test statistics (genomic control, STRUCTURE, Eigenstrat)
Single-SNP analysis (ANOVA, regression)
Gene–gene, gene–environment interaction
Exhaustive evaluation feasable
Candidate epistasis
No
Evolutionary search for interactions
Yes
Traditional statistical methods (regression)
Combinational methods (CPM, gMDR)

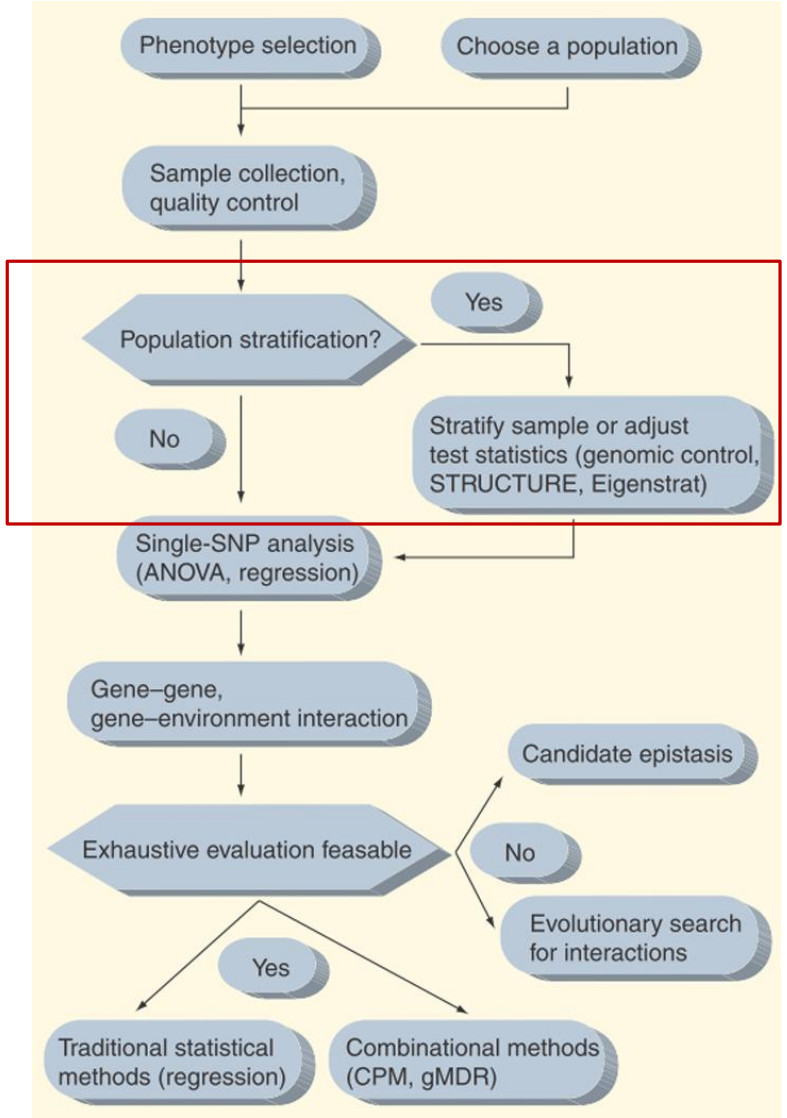


Initialization of pharmacogenomic study

Phenotype Selection - Choose an outcome that is reliably measured and easily replicated. When the outcome of interest is a qualitative trait, test for allele or genotype frequency differences between cases and controls (Case-control study).

QA – Patient compliance.

Choose population – Select subgroup (ethnicity).

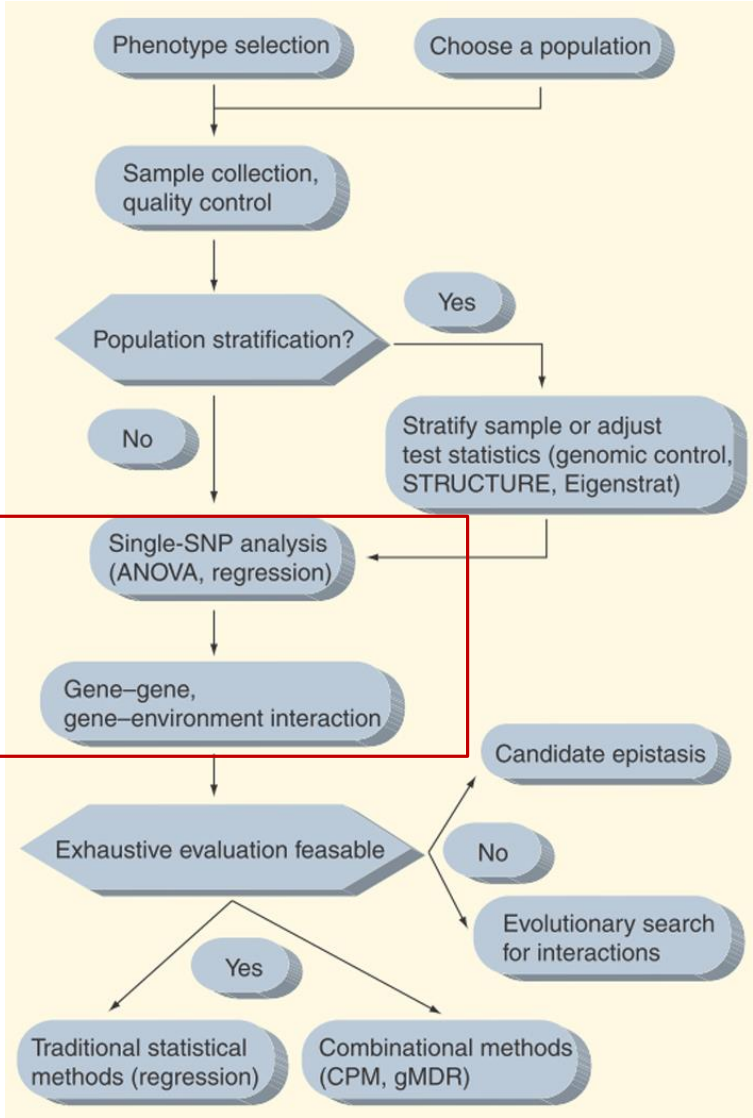


Population Stratification

Population stratification occurs in the presence of undetected population structure whereby study patients differ in both genetic ancestry and phenotype.

Association could be found due to the underlying structure of the population and not a disease associated locus.

Eigenstrat - uses principal components analysis to explicitly model ancestrial differences between cases and controls along continuous axes of variation; minimizing spurious associations while maximizing power to detect true associations.



ANOVA/Regression Analysis

Good for single SNP analysis.

ANOVA tests for significant differences in the mean value of a quantitative outcome between individuals in groups based on genotype.

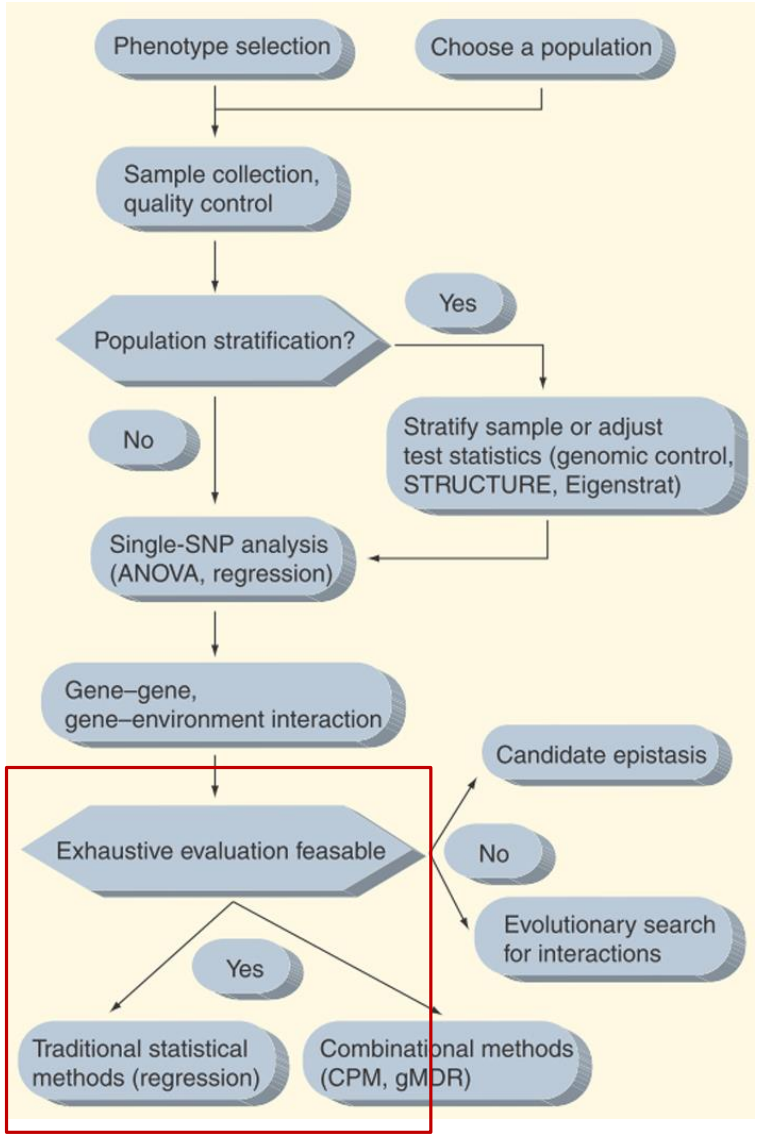
Linear regression allows very specific tests for both gene-gene and gene-environment interaction.

Assumes:

That the data is normally distributed.

Homogeneity of variance, which means that the variance among the groups should be approximately equal.

Observations are independent of each other.



Exhaustive Evaluation

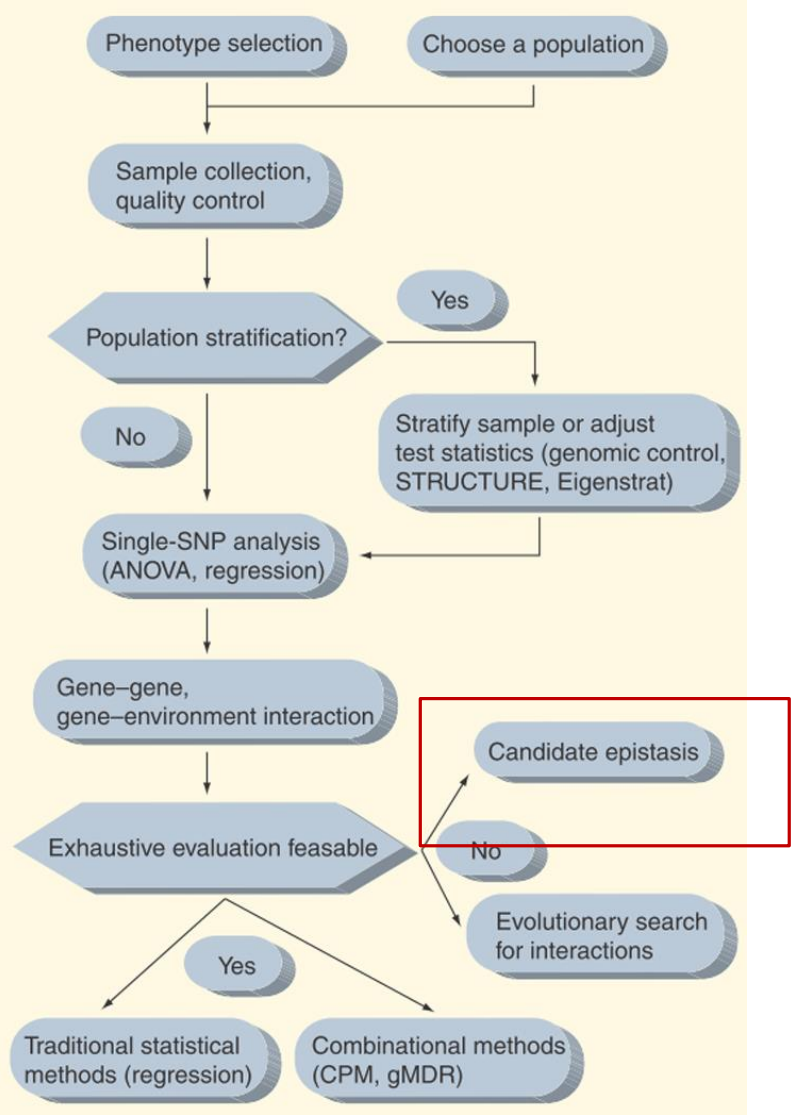
Evaluate every possible outcome between drug response and every combination of genetic and environmental exposures.

Fitting ANOVA or linear regression models to every possible 2-, 3-, or n-way combination SNPs

When interactions among multiple genetic and/or environmental components are considered, there are many combinations that are present in only a few individuals or none at all. -> Curse of dimensionality.

gMDR - generalized multifactor dimensionality reduction

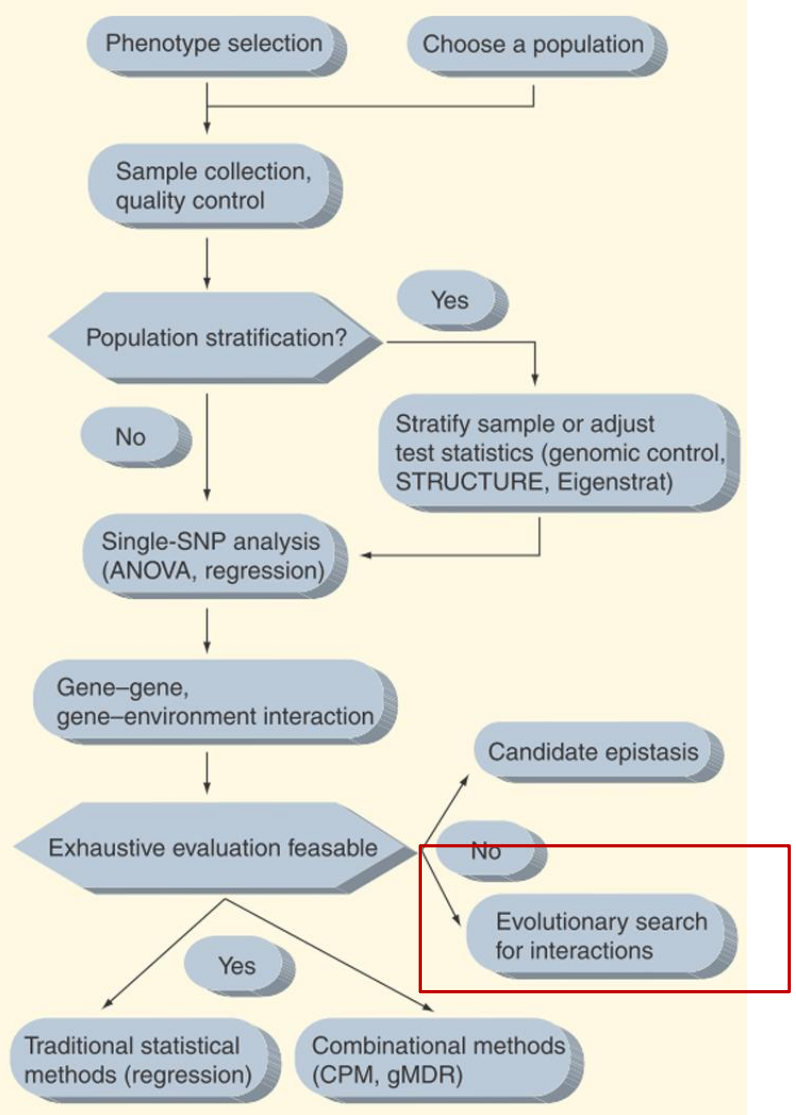
CPM - combinatorial partitioning method



Candidate Epistasis

Assess specific combinations of genetic variants based on prior statistical and biological knowledge.

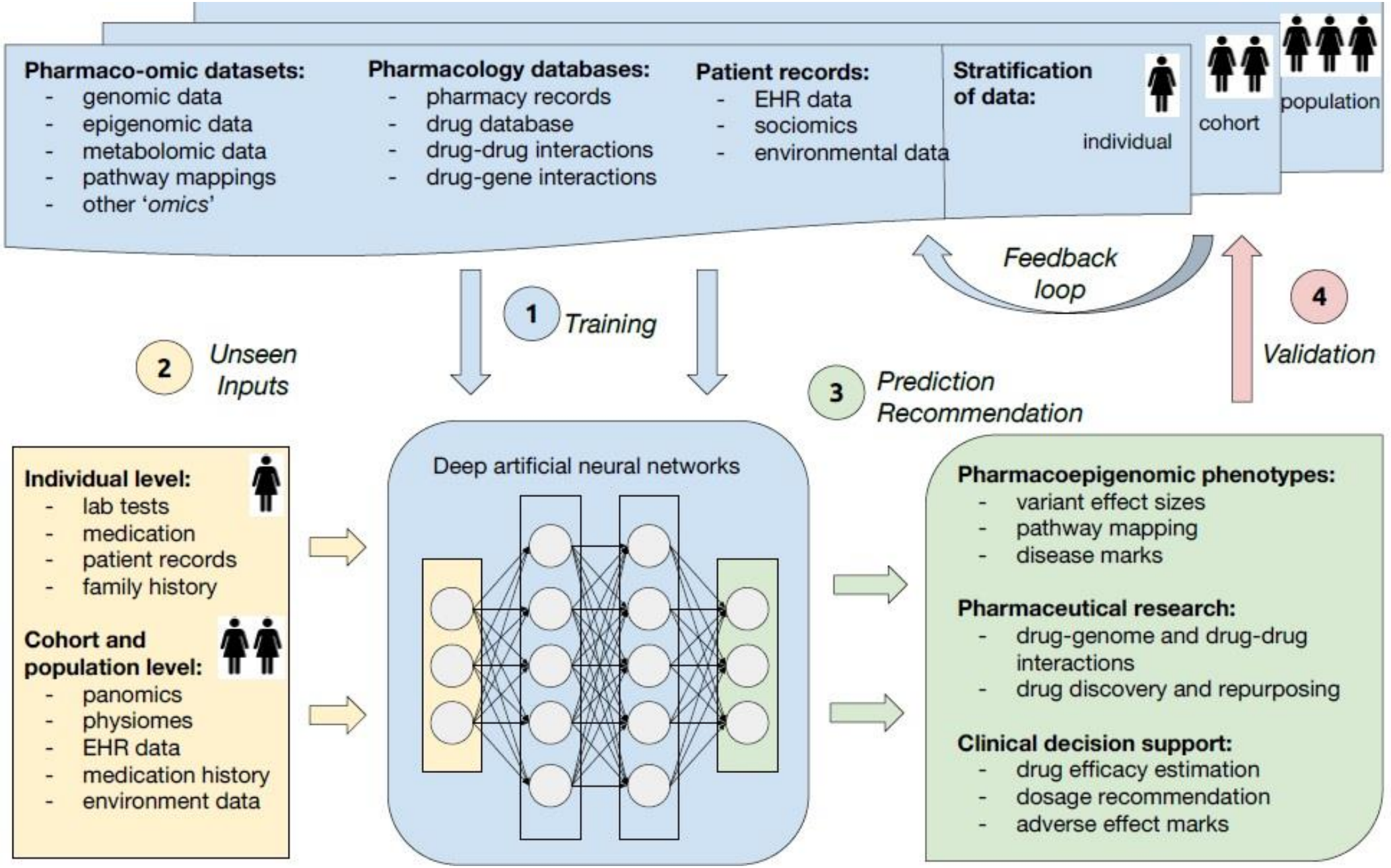
The method creates multi-SNP models based on information from publicly available bioinformatics data sources that can then be tested using logistic or linear regression.



Evolutionary Computing

Define a population of candidate solutions (set outcomes) to a problem and find a model containing influential genes that can explain a large proportion of variance in the outcome.

The candidate solutions will explain more variance in the outcome if the models contain combinations of variables that truly influence the phenotype.


Pharmaco-omic datasets:
- genomic data
- epigenomic data
- metabolomic data
- pathway mappings
- other 'omics'
Pharmacology databases:
- pharmacy records
- drug database
- drug-drug interactions
- drug-gene interactions
Patient records:
- EHR data
- sociomics
- environmental data
Stratification of data:
individual
cohort
population
Feedback loop
1 Training
2 Unseen Inputs
3 Prediction Recommendation
4 Validation
Individual level:
- lab tests
- medication
- patient records
- family history
Cohort and population level:
- panomics
- physiomes
- EHR data
- medication history
- environment data
Deep artificial neural networks
Pharmacoepigenomic phenotypes:
- variant effect sizes
- pathway mapping
- disease marks
Pharmaceutical research:
- drug-genome and drug-drug interactions
- drug discovery and repurposing
Clinical decision support:
- drug efficacy estimation
- dosage recommendation
- adverse effect marks

Future

Many pharmacological outcomes are naturally continuous variables and the full distribution should be considered.

Gene-gene and gene-environment interactions are ubiquitous, and exist even in the absence of an observable phenotype.

Optimal statistical methods will account for interactions between multiple variables.

Replication is important: requirement to provide either statistical replication in an independent sample, or evidence of a functional role for any pharmacogenomic association discovered.

PharmacoGX – R Package

Purpose: To investigate large datasets and assess the reproducibility of data to identify the molecular features that are associated with drug effects.

Main feature:

Integrative analysis of standardized pharmacogenomic datasets from two drug sensitivity datasets.

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