



THE CLINICAL PROBLEM



Standard dose

PGx phenotype: metabolic capacity for a given enzyme



Extensive metabolizers: normal enzyme activity

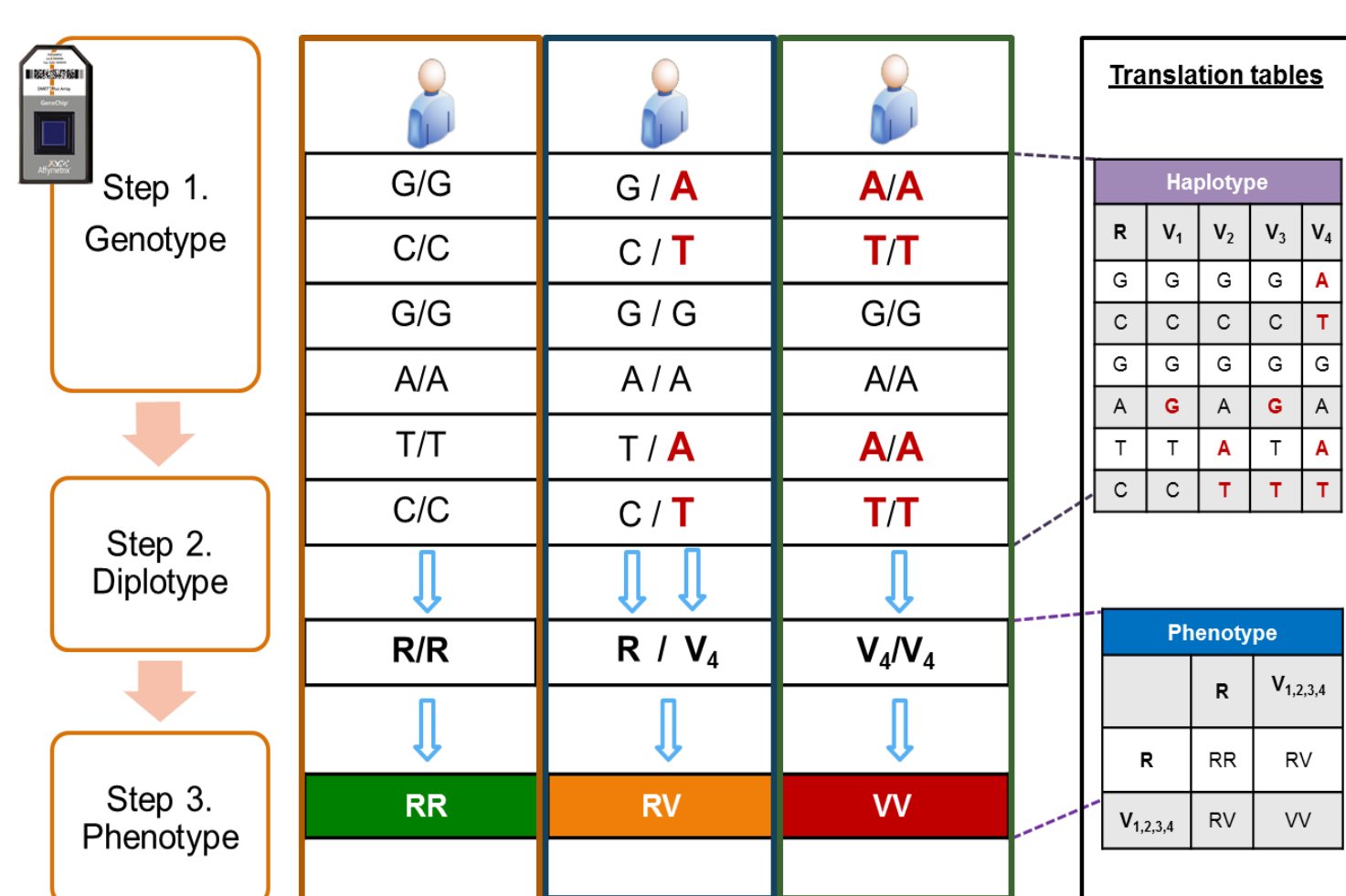
Intermediate metabolizers: decreased enzyme activity

Poor metabolizers: little to no enzyme activity

Ultra rapid metabolizers: increased enzyme activity

PGx Translation Service

METHODOLOGY. We developed an automated **PGx translation algorithm**, which infers metabolic phenotypes from individual genetic (SNP) profiles. For each pharmacogene, and based on available (PharmGKB) haplotype/allele tables, an individual's genotype-profile is **matched** against the available gene-alleles. Next, each inferred diplototype is assigned to a PGx phenotype status, according to available “look up” tables [the algorithm was verified with the Affymetrix® DMET Plus respective translation results]



Glossary.

Pharmacogene - any evidence based gene related to drug Absorption, Distribution, Metabolism, Excretion and Toxicity (ADMET);

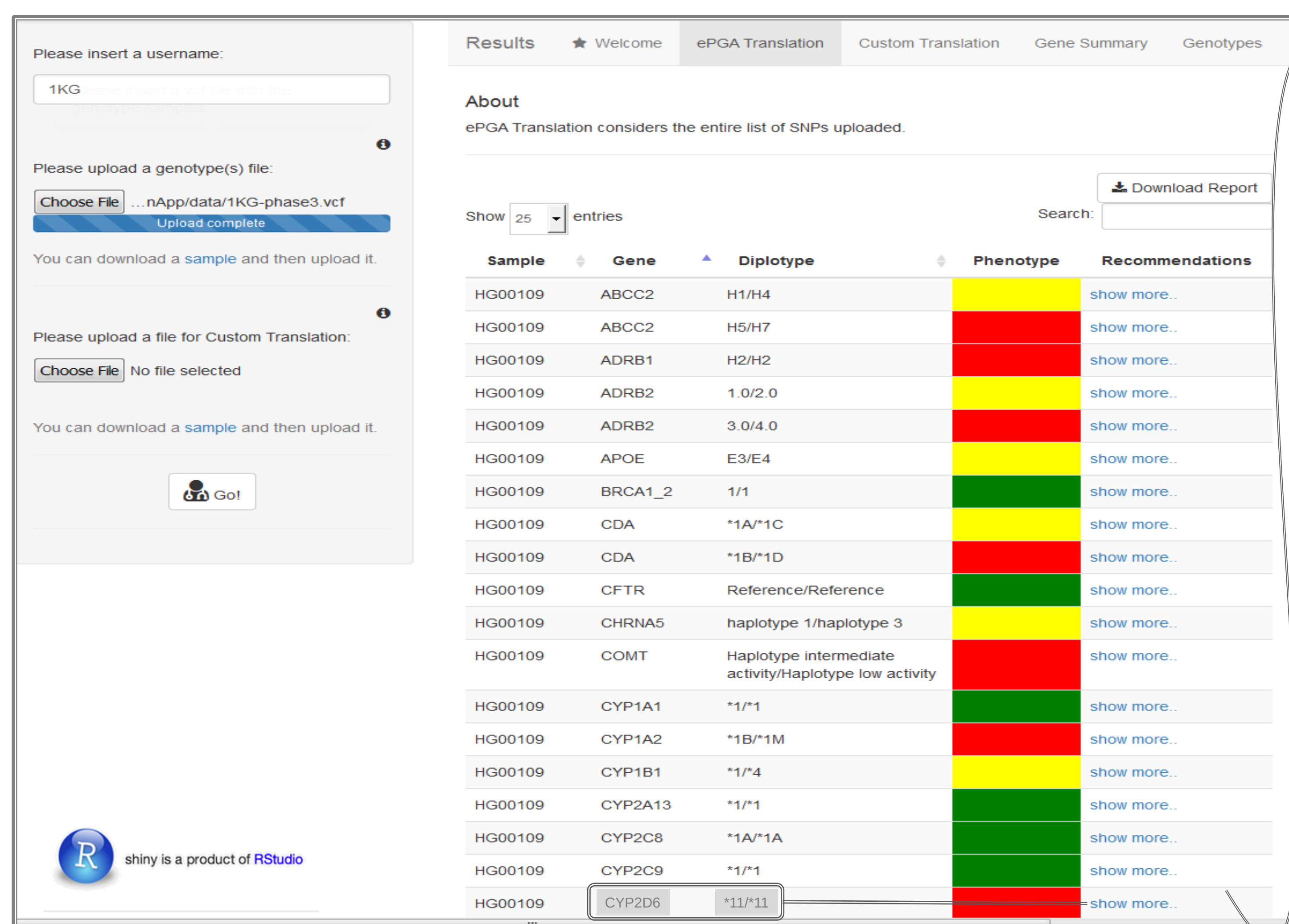
Pharmacogenomic marker - any Single Nucleotide Polymorphism (SNP) present in a pharmacogene locus.

Reference/Reference (R/R) - refers to the combination of two reference (wild-type) haplotypes and corresponds to a ‘normal’ metabolic status.

Reference/Variant (R/V) - refers to the combination of one reference and one variant haplotype (any non wild-type haplotype) and corresponds to an ‘intermediate’ metabolic status.

Variant/Variant (V/V) - refers to any combination of two variant haplotypes that may lead to either a poor or an ultra-rapid metabolic status; an ‘abnormal’ metabolic status.

IMPLEMENTATION. The core of the translation process is implemented in the open-source **R** environment (www.r-project.org) and uses R Studio's **Shiny** web-application framework (<http://shiny.rstudio.com/>) to build its web-based interface.



eMoDiA: electronic Molecular Diagnostic Assistant

	Personalization	Quality of information	Cost	Updatable
Current scientific Knowledge bases	×	✓	✓	×
Commercial Direct To Consumer (DTC) companies	✓	?	×	×
eMoDiA: electronic Molecular Diagnostic Assistant	✓	✓	✓	✓

- To **integrate** heterogeneous PGx information from several valid PGx resources (PharmGKB, dbSNP, Ensembl ...)
- To offer automated **personalized PGx translation** (genotype-to-phenotype) services, linked to drug recommendations
- To provide a user friendly interface for **submitting newly discovered PGx related gene-variants and alleles**

eMoDiA: Explore Service

METHODOLOGY. The **explore** functionality couples drugs, genes and diplotypes with personalized recommendations in a simple database schema. Currently eMoDiA relies on the PharmGKB dosing guidelines. Health professionals or biomedical researchers browse this information through a lightweight web service. eMoDiA shows recommendations that form an expandable tree with user friendly and printable content.



1 Gene(s): 1 selected

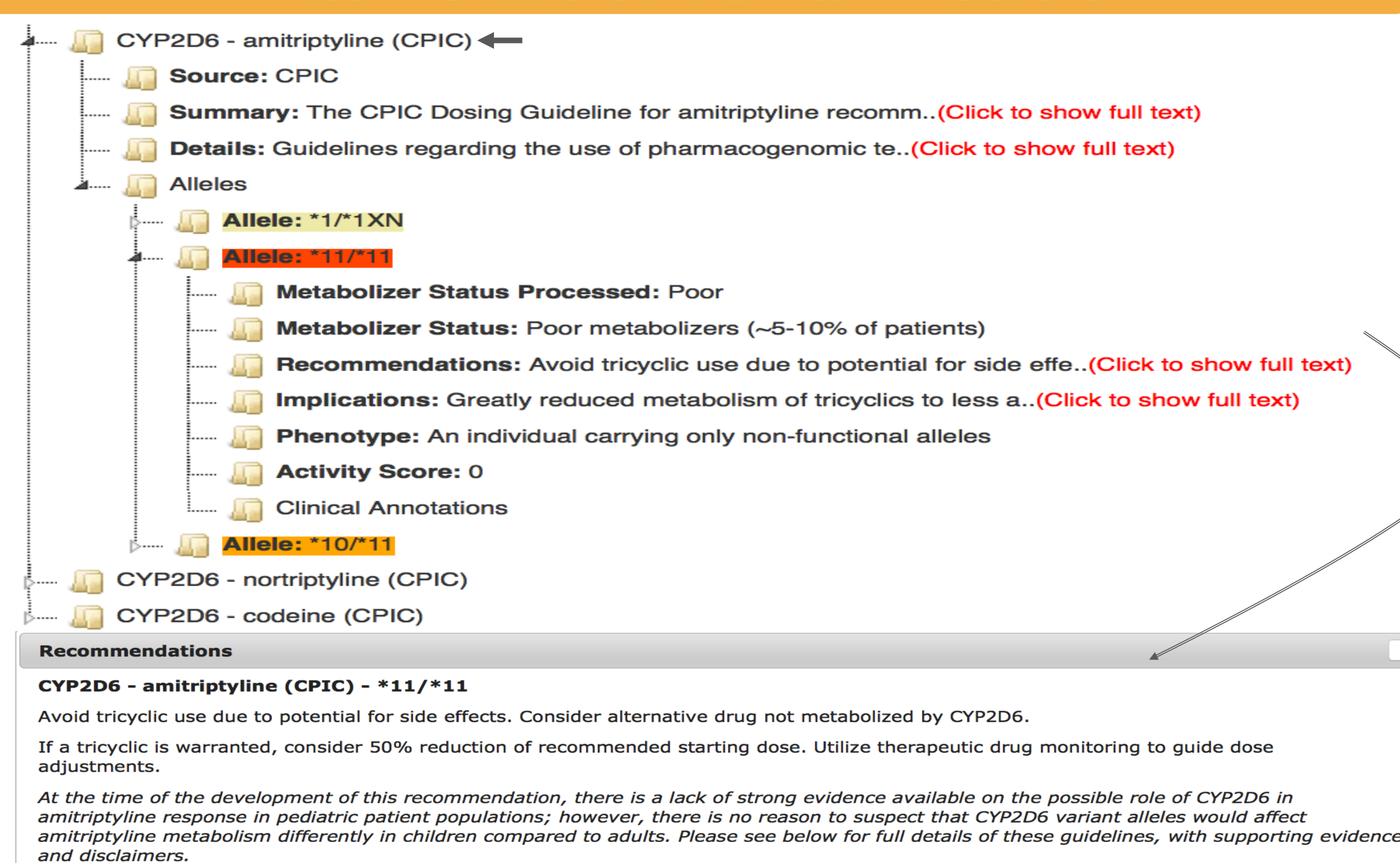
3 Drug(s): 3 selected

3 Metabolizer Status: 3 selected

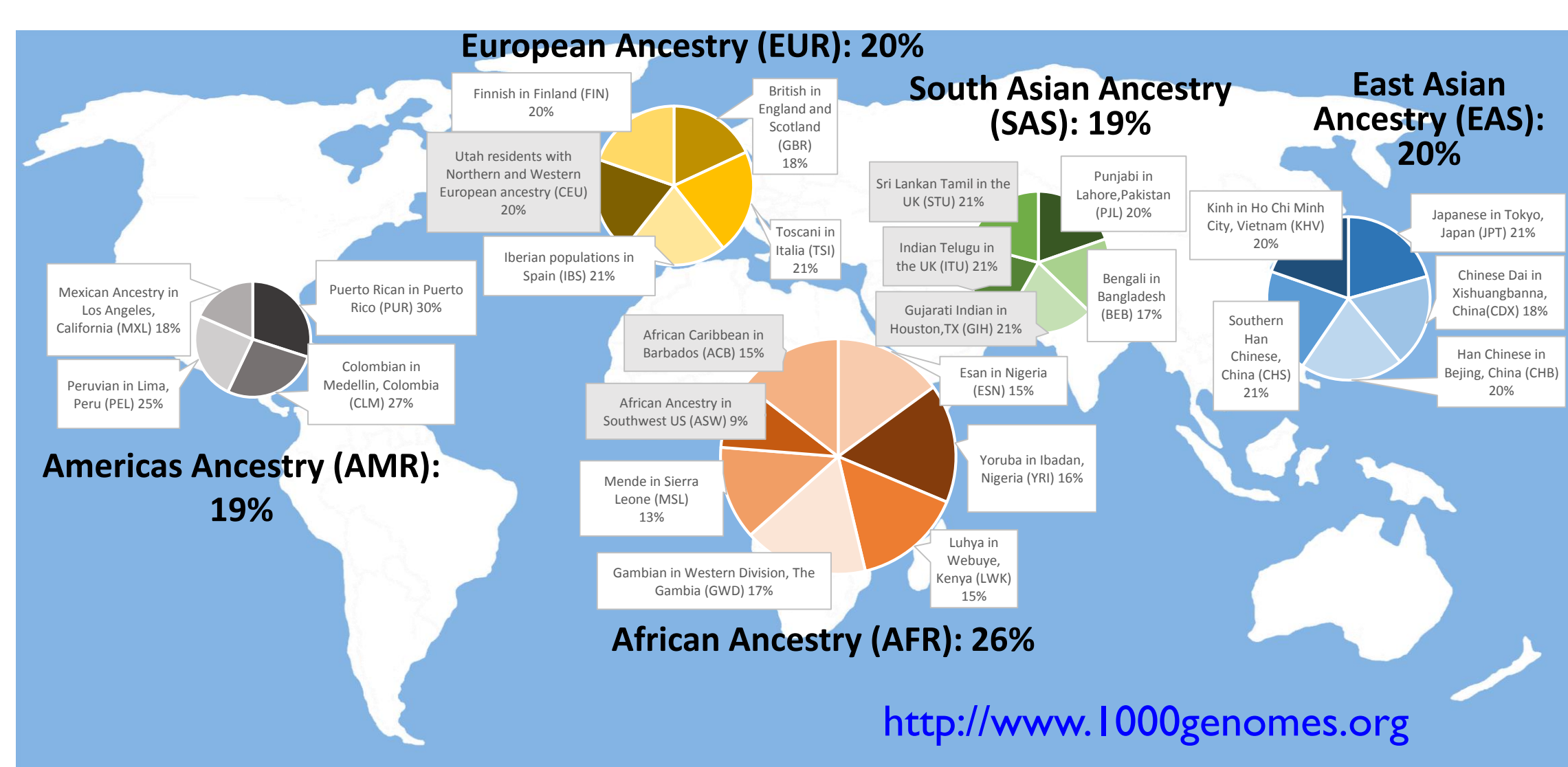
3 Alleles: 3 selected

Show recommendations Clear

Recommendations and Clinical Annotations



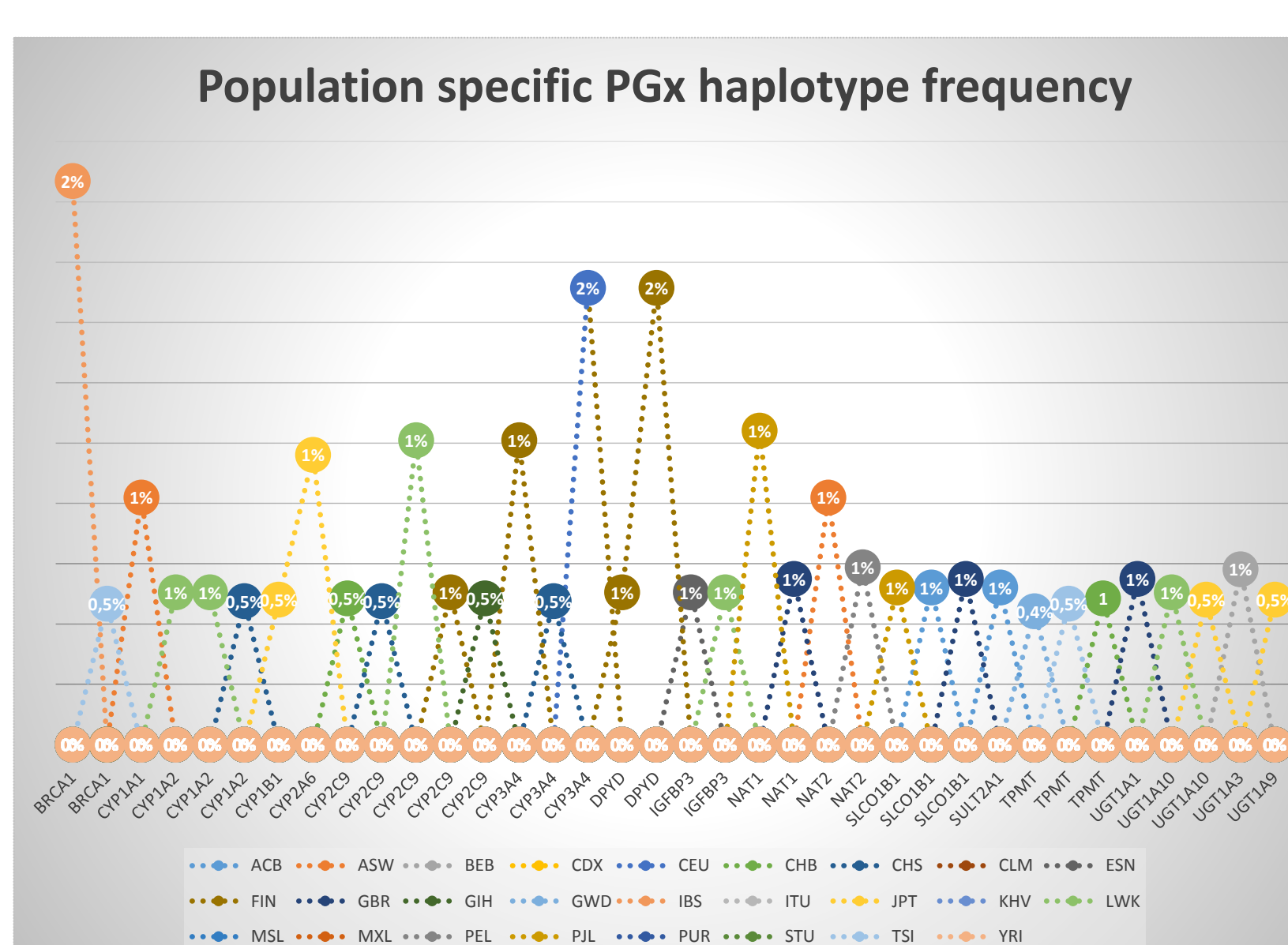
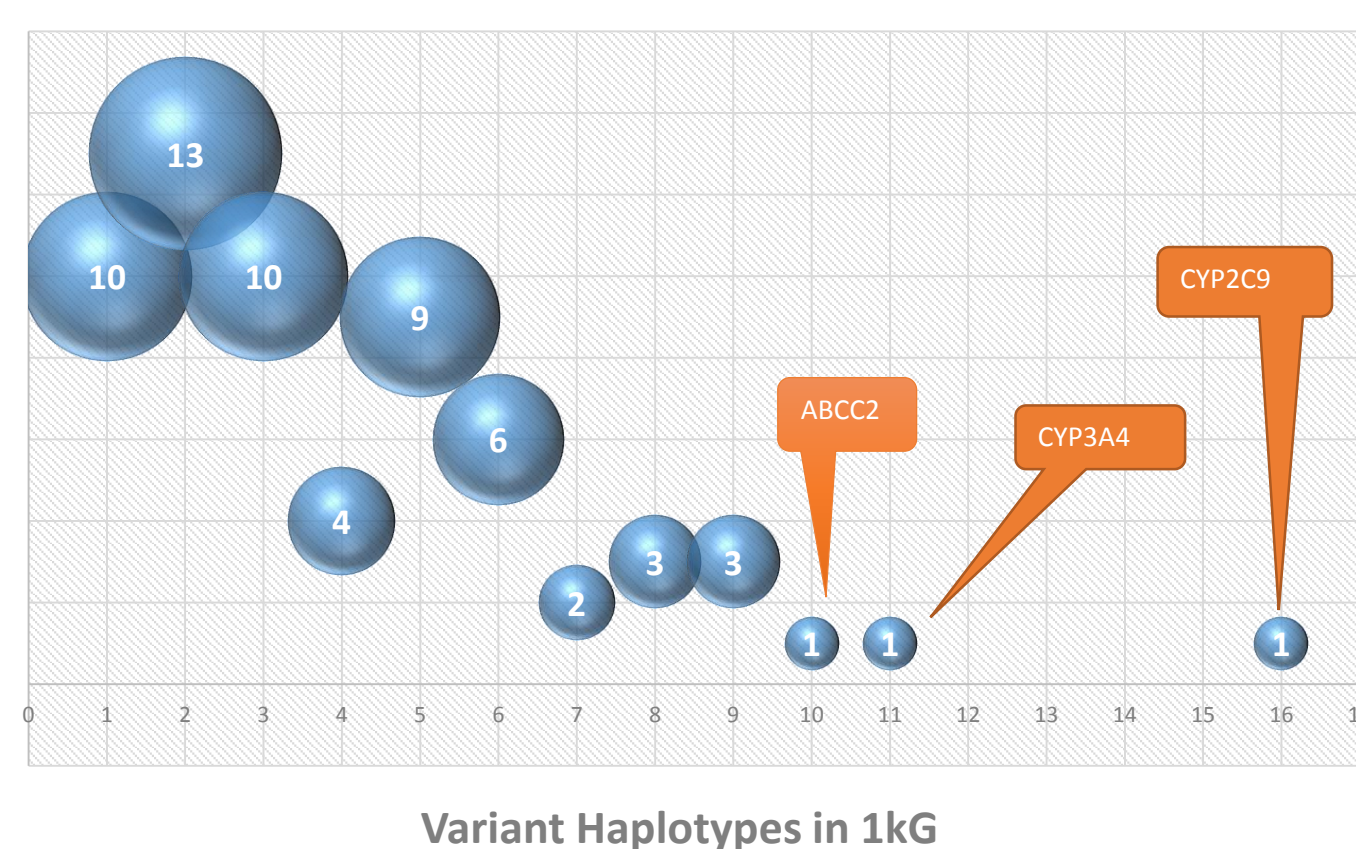
POPULATION PHARMACOGENOMICS ANALYSIS ILLUSTRATES THE IMPORTANCE OF STRATIFIED MEDICINE FOR THE SAFER USE OF EXISTING MEDICINES



❑ The **1000 Genomes (1kG) Project** aims to provide a deep characterization of human genome sequence variation.

❑ **2504 individuals from 26 populations**

❑ **Total variant sites ~80M**



- ❑ **36 PGx haplotypes (~11%) are matched to a single population.**
- ❑ **18 populations (~69%) have at least 1 unique PGx haplotype**
- ❑ **JPTs and FINs match uniquely to four different PGx haplotypes and LWKs to five.**

CONCLUSIONS.

- eMoDiA adequately (sample coverage>90%) assigned PGx phenotypes to 2504 individuals for 33 out of 69 pharmacogenes.
- Statistically significant ($p < 10^{-10}$) phenotypic difference among populations in 29 pharmacogenes
- Potential abnormal metabolism of most individuals in several genes (i.e. ADRB2, LDLR)

