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How to Consider Rare Genetic Variants in Personalized Drug Therapy

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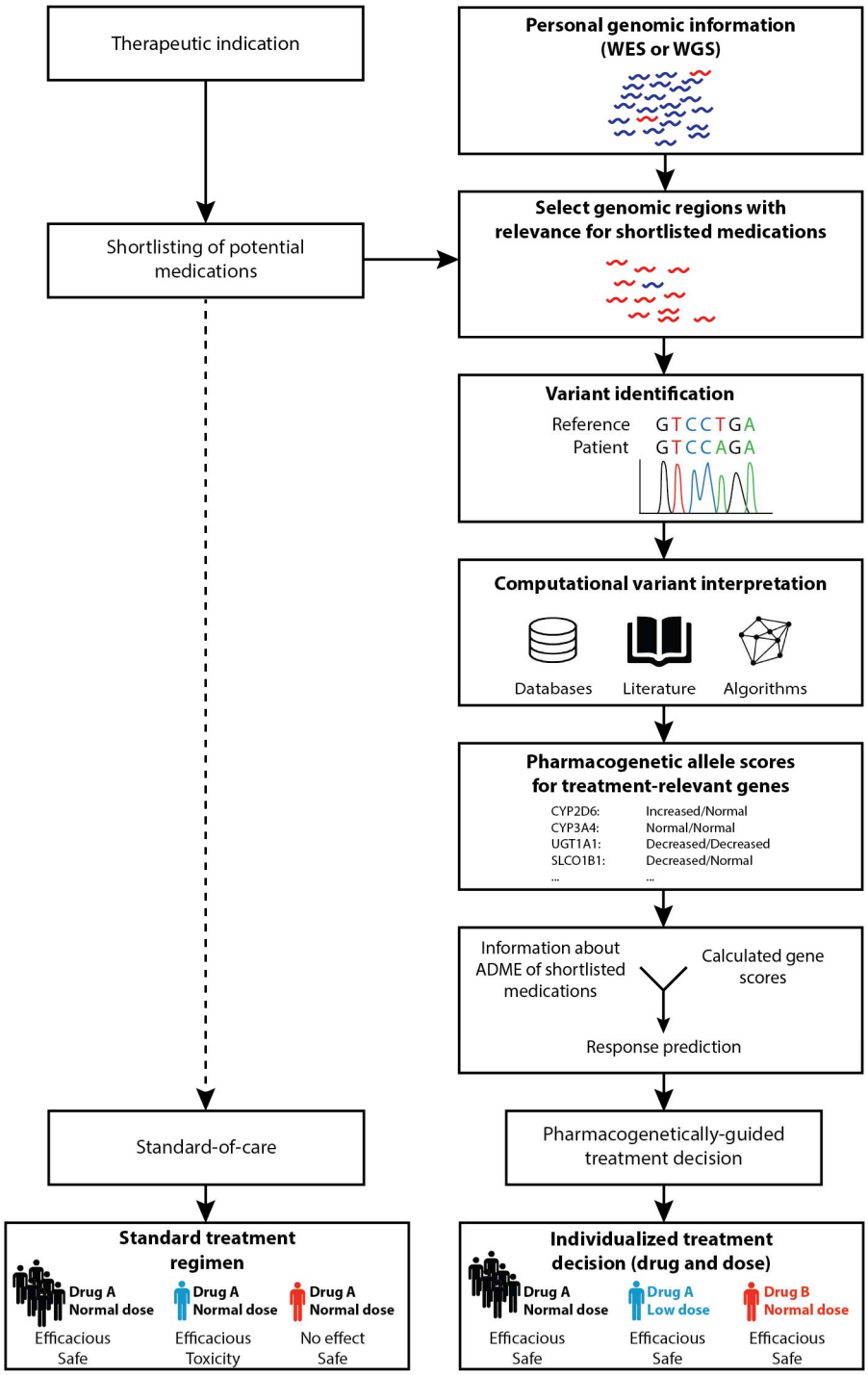
Variability in genes implicated in drug pharmacokinetics or drug response can modulate treatment efficacy or predispose to adverse drug reactions. Research in the last decades revealed a multitude of associations between genotype and drug response, some of which are now included in drug labels. However, in recent years it became evident that the vast majority of the number of genetic variants in genes of importance for drug metabolism, transport and response are rare, with minor allele frequencies <1%.

To understand the global importance of rare pharmacogenetic gene variants, we mapped the genetic variability in 208 pharmacogenes by analyzing exome sequencing data from 60,706 unrelated individuals. To estimate the importance of rare and common genetic variants we developed a functionality prediction framework optimized for pharmacogenetic assessments based on experimental functionality data from 240 pharmacogenetic variant alleles in 22 different ADME genes. Our model achieved 92% sensitivity and 95% specificity for loss-of-function and functionally neutral variants, respectively.

Our analyses reveal that rare pharmacogenetic variants were strongly enriched in mutations predicted to cause functional alterations. For more than half of the pharmacogenes, rare variants account for the entire genetic variability. Each individual harbored on average a total of 40.6 putatively functional variants, rare variants accounting for 10.8% of these. Overall, the contribution of rare variants was found to be highly gene- and drug-specific. Using warfarin, simvastatin, voriconazole, olanzapine and irinotecan as examples, we conclude that rare genetic variants likely account for a substantial part of the unexplained inter-individual differences in drug metabolism phenotypes.

The abovementioned improvements in the performance of computational algorithms to reliably flag functionally deleterious and neutral variants raise hopes that predictions regarding the functionally most important mutations in the different genes of importance for a respective drug treatment can be made based on whole exome or whole genome sequencing data (Figure 1). While multiple challenges still need to be overcome, we suggest that computationally interpreted NGS-data can be of great importance for decision-making regarding choice of drug therapy and dosing regimen in the clinical setting.


Therapeutic indication
Shortlisting of potential medications
Personal genomic information (WES or WGS)
Select genomic regions with relevance for shortlisted medications
Variant identification
Reference GTCCTGA
Patient GTCCAGA
Computational variant interpretation
Databases
Literature
Algorithms
Pharmacogenetic allele scores for treatment-relevant genes
CYP2D6: Increased/Normal
CYP3A4: Normal/Normal
UGT1A1: Decreased/Decreased
SLCO1B1: Decreased/Normal
...
Information about ADME of shortlisted medications
Calculated gene scores
Response prediction
Standard-of-care
Pharmacogenetically-guided treatment decision
Standard treatment regimen
Drug A Normal dose
Efficacious Safe
Drug A Normal dose
Efficacious Toxicity
Drug A Normal dose
No effect Safe
Individualized treatment decision (drug and dose)
Drug A Normal dose
Efficacious Safe
Drug A Low dose
Efficacious Safe
Drug B Normal dose
Efficacious Safe