The roots of pharmacogenetics may date back as early as the 6th century BC, when Pythagoras was said to have recognized that eating fava beans caused illness in some, but not all, individuals.
Luciano di Samòsata nel suo dialogo *Il sogno ovvero il gallo* - Óneiros ἐ ἀλεκτρυὸν, 4-5:

Gallo: Hai sentito parlare di un certo Pitagora figlio di Mnesarco, di Samo?
Micillo: Intendi il sofista, l’esaltato che aveva fatto la regola di non assaggiare la carne e di non mangiare le fave (eliminando così dalla tavola un cibo che a me piace moltissimo)...?
In the 1940s, the immunochemist William Boyd noted that in contrast to Mediterranean populations, native Britons almost never developed hemolytic anemia after ingestion of fava beans; he suggested a genetic difference as the probable explanation. It is now known that the hemolytic anemia associated with ingestion of fava beans, which may also occur with a variety of pharmacologic agents, is due to X-linked glucose-6-phosphate dehydrogenase deficiency (G6PD).
Although some progress has been made in the study of mechanisms of drug allergy, little was known until recently about the pathogenesis of hypersusceptibility reactions and hyposusceptibility reactions. Data are available now which suggest the reactions of this type may be caused by otherwise genetic traits or enzyme deficiencies.
How an individual genetic inheritance affects the body’s response to drug...
After single oral doses, rates of elimination of ethanol, phenylbutazone, antipyrine, and dicumarol were measured in the plasma of identical and fraternal twins. In our twins, large individual differences in rates of elimination of ethanol (twofold), antipyrine (threelfold), phenylbutazone (sixfold), and dicumarol (tenfold) were almost exclusively under genetic control and under "basal" conditions were influenced negligibly by environmental factors. Each subject's rate of drug elimination was a highly reproducible value.

Annals New York Academy of Sciences 1971
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• Farmacodinamica
• Reazioni idiosincrasiche
• Variabili genetiche condizionanti la patogenesi della malattia
Figure 1. Polygenic Determinants of Drug Response.

The potential effects of two genetic polymorphisms are illustrated, one involving a drug-metabolizing enzyme (top) and the second involving a drug receptor (middle), depicting differences in drug clearance (or the area under the plasma concentration–time curve [AUC]) and receptor sensitivity in patients who are homozygous for the wild-type allele (WT/WT), heterozygous for one wild-type and one variant (V) allele (WT/V), or have two variant alleles (V/V) for the two polymorphisms. At the bottom are shown the nine potential combinations of drug-metabolism and drug-receptor genotypes and the corresponding drug-response phenotypes calculated from data at the top, yielding therapeutic indexes (efficacy:toxicity ratios) ranging from 13 (65 percent:5 percent) to 0.125 (10 percent:80 percent).
## Table 2. Genetic Polymorphisms in Disease-Modifying or Treatment-Modifying Genes That Can Influence Drug Response.*

<table>
<thead>
<tr>
<th>Gene or Gene Product</th>
<th>Disease or Response Association</th>
<th>Medication</th>
<th>Influence of Polymorphism on Drug Effect or Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adducin</td>
<td>Hypertension</td>
<td>Diuretics</td>
<td>Myocardial infarction or strokes(^6^9)</td>
</tr>
<tr>
<td>Apolipoprotein E (APOE)</td>
<td>Progression of atherosclerosis, ischemic cardiovascular events</td>
<td>Statins (e.g., simvastatin)</td>
<td>Enhanced survival(^7^0,7^1)</td>
</tr>
<tr>
<td>Apolipoprotein E (APOE)</td>
<td>Alzheimer’s disease</td>
<td>Tacrine</td>
<td>Clinical improvement(^7^2)</td>
</tr>
<tr>
<td>HLA</td>
<td>Toxicity</td>
<td>Abacavir</td>
<td>Hypersensitivity reaction(^7^3,7^4)</td>
</tr>
<tr>
<td>Cholesterol ester transfer protein (CETP)</td>
<td>Progression of atherosclerosis</td>
<td>Statins (e.g., pravastatin)</td>
<td>Slowing of progression of atherosclerosis by pravastatin(^7^5)</td>
</tr>
<tr>
<td>Ion channels (HERG, KvLQT1, Mink, MiRP1)</td>
<td>Congenital long-QT syndrome</td>
<td>Erythromycin, terfenadine, cisa-</td>
<td>Increased risk of drug-induced torsade de pointes(^7^6-7^8)</td>
</tr>
<tr>
<td>Methylguanine methyltransferase (MGMT)</td>
<td>Glioma</td>
<td>Carmustine</td>
<td>Response of glioma to carmustine(^6^3)</td>
</tr>
<tr>
<td>Parkin</td>
<td>Parkinson’s disease</td>
<td>Levodopa</td>
<td>Clinical improvement and levodopa-induced dyskinesias(^7^9)</td>
</tr>
<tr>
<td>Prothrombin and factor V</td>
<td>Deep-vein thrombosis and cerebral-vein thrombosis</td>
<td>Oral contraceptives</td>
<td>Increased risk of deep-vein and cerebral-vein thrombosis with oral contraceptives(^8^0)</td>
</tr>
<tr>
<td>Stromelysin-1</td>
<td>Atherosclerosis progression</td>
<td>Statins (e.g., pravastatin)</td>
<td>Reduction in cardiovascular events by pravastatin (death, myocardial infarction, stroke, angina, and others); reduction in risk of repeated angioplasty(^8^1)</td>
</tr>
</tbody>
</table>

* The examples shown are illustrative and not representative of all published studies, which exceed the scope of this review.
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The influence of genetic polymorphisms in cytochrome P450 enzymes CYP2D6, CYP2C19 and CYP2C9, thiopurine S-methyltransferase (TPMT) and N-acetyltransferase type 2 (NAT2) is expressed as subpopulation-specific dosages, according to the difference in pharmacokinetic parameters from clinical studies. The dose adjustments illustrated by the bars in this graph are based on differences in dose-related pharmacokinetic parameters (clearance, AUC, STEADY STATE CONCENTRATION) caused by particular genotypes and are calculated using the methods described earlier. Substantial adjustments need to be made to drug dose to achieve the same level of drug exposure in individuals with different genotypes.

AUC: area under the curve; EM: extensive metabolizer; IA: intermediate acetylator; IM: intermediate metabolizer; PM: poor metabolizer; RA: rapid acetylator; SA: slow acetylator; UM: ultra-rapid metabolizer.

Effect of variation in CYP2D6 metabolism with clinical response to two therapeutic agents

<table>
<thead>
<tr>
<th>Codeine</th>
<th>Pain relief</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EM</strong></td>
<td>C → M</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>PM</strong></td>
<td>C → C</td>
<td>No</td>
</tr>
<tr>
<td><strong>UM</strong></td>
<td>C → M → M</td>
<td>Yes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nortriptyline</th>
<th>Relief of depression</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EM</strong></td>
<td>N → I</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>PM</strong></td>
<td>N → N → N</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>UM</strong></td>
<td>N → I → I</td>
<td>No</td>
</tr>
</tbody>
</table>

Based upon genetic make-up and the resultant ability to metabolize therapeutic agents, individuals can be classified as extensive (normal) metabolizers (EM), poor metabolizers (PM), or ultrarapid metabolizers (UM). Since codeine is metabolized into an active agent (morphine), poor metabolizers may require increased dosing for a given therapeutic effect, while ultrarapid metabolizers may build up excessive levels of morphine, leading to adverse sequelae. Conversely, nortriptyline is the active therapeutic agent and is metabolized to an inactive form. In this case poor metabolism leads to adequate therapy but an increased incidence of side effects, while extensive metabolizers may require increased dosing for therapeutic effect.

C: codeine; M: morphine; N: nortriptyline; I: inactive nortriptyline; EM: extensive metabolizers; PM: poor metabolizers; UM: ultrarapid metabolizers.

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Review article

CYP2D6 and CYP2C19 genotype-based dose recommendations for antidepressants: a first step towards subpopulation-specific dosages


Objective: This review aimed to provide distinct dose recommendations for antidepressants based on the genotypes of cytochrome P450 enzymes CYP2D6 and CYP2C19. This approach may be a useful complementation to clinical monitoring and therapeutic drug monitoring.

Method: Our literature search covered 32 antidepressants marketed in Europe, Canada, and the United States. We evaluated studies which had compared pharmacokinetic parameters of antidepressants among poor, intermediate, extensive and ultrarapid metabolizers.

Results: For 14 antidepressants, distinct dose recommendations for extensive, intermediate and poor metabolizers of either CYP2D6 or CYP2C19 were given. For the tricyclic antidepressants, dose reductions around 50% were generally recommended for poor metabolizers of substrates of CYP2D6 or CYP2C19, whereas differences were smaller for the selective serotonin reuptake inhibitors.

Conclusion: We have provided preliminary average dose suggestions based on the phenotype or genotype. This is a first attempt to apply the new pharmacogenetics to suggest dose-regimens that take the differences in drug metabolic capacity into account.

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Key words: polymorphism; antidepressant therapy; pharmacogenetics; cytochrome P-450; CYP2D6; CYP2C19

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Thiopurine s-methyltransferase (TPMT) is responsible for the metabolism of the class of therapeutic compounds called thiopurines (eg, azathioprine, mercaptopurine [6-MP]). Variation in the TPMT gene can result in functional inactivation of the enzyme, and a markedly increased risk of life-threatening myelosuppression. For this reason, TPMT testing is recommended by the United States Food and Drug Administration prior to treatment.
Many physicians consider that TPMT genotyping is mandatory prior to the administration of thiopurines for treatment of inflammatory and autoimmune disorders, this is not a universal viewpoint.

The prevalence of homozygous variants among Caucasians is only about 1 in 300; it is even lower in African and Asian populations. Therefore, testing is only applicable to a very small percent of the population. Furthermore, the majority of patients who develop myelosuppression while taking azathioprine do not have detectable TPMT gene mutations.
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Effect of VKORC1 Haplotypes on Transcriptional Regulation and Warfarin Dose

Mark J. Rieder, Ph.D., Alexander P. Reiner, M.D., M.P.H., Brian F. Gage, M.D., M.Sc., Deborah A. Nickerson, Ph.D., Charles S. Eby, M.D., Howard L. McLeod, Pharm.D., David K. Blough, Ph.D., Kenneth E. Thummel, Ph.D., David L. Veenstra, Pharm.D., Ph.D., and Allan E. Rettie, Ph.D.
Figure 1. Effect of VKORC1 Haplotype Combination on Clinical Warfarin Dose.

As shown in the upper panel, common haplotypes (H1, H2, H7, H8, and H9) were clustered with use of the UPGMA method (unweighted pair group method with arithmetic mean); they formed two distinct evolutionarily distant groups, designated A (comprising H1 and H2) and B (comprising H7, H8, and H9). Eight single-nucleotide polymorphisms (SNPs) are labeled at the nodes of the tree, and four SNP sites (shown in boldface) were used to discriminate between each branch and to distinguish groups A and B. Asterisks indicate correlated SNP sets that were significantly associated with warfarin dose. Group A was associated with a low warfarin dose and group B a high warfarin dose. As shown in the middle panel, patients in the primary population were genotyped and assigned a VKORC1 haplotype combination (A/A, A/B, or B/B). The patients were further classified according to CYP2C9 genotype (the wild type or either the *2 or *3 variant). The total numbers of patients having a group A combination, a group B combination, or both were 182 (all patients), 124 (wild-type CYP2C9), and 58 (variant CYP2C9). Four patients could not be assigned either to group A or to group B. As shown in the bottom panel, 357 patients from the replication sample were genotyped and grouped as were those in the primary patient population; 233 had wild-type CYP2C9 and 124 variant CYP2C9. The asterisks in the bottom two panels denote P<0.05 for the comparison with combination A/A and the daggers P<0.05 for the comparison with combination A/B. The T bars represent standard errors.
Estimation of the Warfarin Dose with Clinical and Pharmacogenetic Data

The International Warfarin Pharmacogenetics Consortium*
Figure 2. Percentage of Patients with Dose Estimates within 20% of the Actual Dose, as Derived with the Use of a Pharmacogenetic Algorithm, a Clinical Algorithm, and a Fixed-Dose Approach.

The dose estimates are shown according to three actual-dose groups: low-dose (≤21 mg per week), intermediate-dose (>21 to <49 mg per week), and high-dose (≥49 mg per week). The fixed dose was 35 mg per week. With the fixed-dose approach, none of the estimates for the patients in the low-dose and high-dose groups were within 20% of the actual dose. Panel A shows data for the validation cohort (1009 patients), and Panel B for the derivation-plus-validation cohorts (5052 patients).
Should We Be Applying Warfarin Pharmacogenetics to Clinical Practice? No, Not Now

Michael H. Rosove, MD, and Wayne W. Grody, MD, PhD

**Key Summary Points**

Certain single-nucleotide polymorphisms of the cytochrome P450 CYP2C9 and vitamin K epoxide reductase complex subunit 1 (VKORC1) genes influence warfarin metabolism and sensitivity.

The U.S. Food and Drug Administration has modified warfarin labeling to suggest, but not mandate, consideration of pharmacogenetic testing of these genes; the test is now commercially available.

Testing predicts only about one third of all dosing variations.

The value and cost-effectiveness of genetic testing to reduce bleeding or thrombosis rates remain unknown.

Consideration of clinical factors that influence dosing, conscientious prothrombin time monitoring, and sage dosage adjustment remain extremely important in warfarin management.

Further study is required before routine warfarin pharmacogenetic testing can be recommended.
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Abacavir is a nucleoside analog with potent activity against HIV; however, a proportion of patients develop severe hypersensitivity reactions to this drug.
ABACAVIR e ADR

- Febbre
- Cefalea, vertigine
- Nausea, vomito, diarrea
- Dispnea e tosse
- Rash cutaneo
- Tachicardia, ipotensione

- Patch test per conferma immunologica di ADR
Abacavir hypersensitivity is associated with carriage of the major histocompatibility complex (MHC) class I allele HLA-B*5701. Presentation of the peptide-HLA complex on an antigen-presenting cell to the receptor of an abacavir-specific CD8+ T-cell activates the release inflammatory cytokines, resulting in the clinical syndrome of acute hypersensitivity syndrome.
Genetic variations in HLA-B region and hypersensitivity reactions to abacavir


Hypersensitivity to abacavir affects about 4% of patients who receive the drug for HIV-1 infection. We did a retrospective, case-control study to identify multiple markers in the vicinity of HLA-B associated with hypersensitivity reactions. HLA-B57 was present in 39 (46%) of 84 patients versus four (4%) of 113 controls (p<0.0001). However, because of low numbers of women and other ethnic groups enrolled, these findings relate largely to white men. The lower sensitivity of HLA-B57 for predicting hypersensitivity to abacavir identified in this study compared with a previous report highlights that predictive values for markers will vary across populations. Clinical monitoring and management of hypersensitivity reactions among patients receiving abacavir must remain unchanged.

Lancet 2002; 359: 1121–22
The main benefit of screening, regardless of race, is that it identifies the majority of the population to whom it is safe to administer abacavir. Although screening necessarily excludes some patients from abacavir therapy who would have tolerated the drug, this is compensated by the fall in false positive clinical diagnoses achieved in an open screening population.
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DRUG THERAPY

Trastuzumab — Mechanism of Action and Use in Clinical Practice

Clifford A. Hudis, M.D.

Overexpression of human epidermal growth factor receptor type 2 (HER2, also referred to as HER2/neu or ErbB-2), a 185-kD receptor first described more than two decades ago, occurs in 20 to 30% of invasive breast carcinomas. In general, patients with breast-cancer cells that overexpress this receptor or that have a high copy number of its gene have decreased overall survival and may have differential responses to a variety of chemotherapeutic and hormonal agents. Thus, strategies to target HER2 appear to be important in treating breast cancer. One such medication is trastuzumab (Herceptin, Genentech), a humanized monoclonal antibody. Trastuzumab binds to the extracellular juxtamembrane domain of HER2 and inhibits the proliferation and survival of HER2-dependent tumors. It is approved by the Food and Drug Administration (FDA) for patients with invasive breast cancers that overexpress HER2. This review considers trastuzumab’s mechanism of action and its clinical value.
Several guideline bodies, including the American Society of Clinical Oncology (ASCO), the National Comprehensive Cancer Network (NCCN), and the National Academy of Clinical Biochemistry recommend routine testing of HER2 expression on newly diagnosed and metastatic breast cancers since 2001.
Limiti nel disegno degli studi (carenza di RCT prospettici e eterogeneità tra gli studi)

Correlazione tra genotipo e fenotipo

Considerazioni etiche

Carenza di studi che valutino il rapporto costo-beneficio

Basso numero di test farmacogenetici disponibili e carenza di linee guida che ne regolino l’implementazione
Circumstances that favor cost effectiveness of a pharmacogenetic test include:

A high prevalence of the genetic variant of interest in the target population, a good correlation between phenotype and genotype, satisfactory diagnostic test criteria, a disease that is associated with significant morbidity or mortality if left untreated, and a significant reduction in adverse drug reactions resulting from testing.

Despite the multitude of pharmacogenetic association studies in the literature, relatively few cost-effective analyses have been performed.

There are only limited data on the rate at which pharmacogenetic testing actually prevents clinically significant adverse drug reactions.

The price of pharmacogenetic tests is likely to drop continuously over the next few years.
CONCLUSIONI
Pharmacogenetic testing is available in some areas in conjunction with certain drug classes, and may enable physicians to understand why patients respond differently to various drugs and to make better decisions about therapy.

However, the goal of "individualized therapy" based upon pharmacogenetic testing has yet to be realized.

Despite the promise of a growing body of research relating to pharmacogenetics and its impact on drug response, and FDA guidelines as to the use of genetic markers to guide therapy for a variety of agents use of these tests is not widespread with a few notable exceptions.