

The information below can help you understand and apply the results of the **DNA Prescription Drug Reaction Test** currently offered by Genelex. Our tests spot individual genetic variants in the four most important drug-metabolizing enzymes: Cytochrome P-450's CYP2D6, CYP2C9, CYP2C19, NAT2 and CYP1A2.

More than half of the population has one or more serious defects in the genes coding for these enzymes. Recent research shows that genetic variation in the drug metabolizing system is the single most important factor affecting a patient's response to drugs. The information Genelex provides can help you determine the appropriateness and dosage of roughly a third of all commonly prescribed drugs. (See attached chart.)

Testing for CYP2D6, CYP2C9 and CYP2C19 places individuals in one of four categories:

- **Extensive Metabolizers (EM)** represent the norm for metabolic capacity. Genotypes consistent with the EM phenotype include two active forms of the gene producing the drug metabolizing enzyme and therefore possess the full complement of drug metabolizing capacity. Generally, extensive metabolizers can be administered drugs which are substrates of the enzyme following standard dosing practices.
- **Intermediate Metabolizers (IM)** may require lower than average drug dosages for optimal therapeutic response for the majority of medications, prodrugs such as tamoxifen will require higher doses. In addition, multiple drug therapy should be monitored closely. Genotypes consistent with the IM phenotype are those with only one active form of the gene producing the drug metabolizing enzyme and therefore have reduced metabolic capacity.
- **Poor Metabolizers (PM)** are at increased risk of drug-induced side effects due to diminished drug elimination or lack of therapeutic effect resulting from failure to generate the active form of the drug. Genotypes consistent with the PM phenotype are those with no active genes producing the drug metabolizing enzyme. These individuals have a deficiency in drug metabolism.
- **Ultra-extensive Metabolizers (UM)** may require an increased dosage due to higher than normal rates of drug metabolism for the majority of medications, prodrugs such as tamoxifen will require lower doses. Simultaneously treating with medication that inhibits metabolism has also proven effective. Genotypes consistent with UM phenotype include three or more active genes producing the drug metabolizing enzyme and therefore have increased metabolic capacity.

Dose Adjustment Chart for IM and PM Genotypes

Best described Pharmacogenetic cases

Medication	Potential characteristic	Enzyme/ Protein	Potential therapeutic modification
Tricyclic Antidepressants	Impaired metabolism	CYP2D6 / CYP2C19	Reduce dose to 20 - 60% of standard dosages based on genotype
Warfarin and other coumarin derivatives	Impaired metabolism	CYP2C9	Reduce dose to 20 - 60% of standard dosages based on genotype
Glipizide and other sulfonylureas	Impaired metabolism	CYP2C9	Reduce dose to 20 - 60% of standard dosages based on genotype
Phenytoin	Impaired metabolism	CYP2C9	Reduce dose to 20 - 60% of standard dosages based on genotype
Codeine	Impaired conversion to morphine	CYP2D6	Avoid in subjects with enzyme deficiency

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Hours 7:00 AM to 6:00 PM PST, 10:00 AM to 9:00 PM EST, fax 206-219-4000,

Genelex Corporation, 3000 First Avenue, Suite One, Seattle, WA 98121

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Cytochrome P-450 2D6

Phenotype prevalence is 10 % PM, 7% UM, and 35% IM.

Therapy Modification

PM - Avoid medications that are altered to their active form through 2D6, such as opioids. (For instance, 10% of a codeine dose is transformed to morphine through demethylation in the liver.) If you are uncertain, contact the drug manufacturer or look up the pharmacology data in the package insert. For assistance, feel free to contact us.

Reduce dose to 20 - 60% of standard dosages for medications that are administered in their active form and deactivated through 2D6 as are many antidepressants. (Desipramine, for example, is absorbed from the gastrointestinal tract following oral administration and is extensively bound to tissue and plasma proteins in the order of 90-95%. It is inactivated by hydroxylation and by further demethylation in the liver.) If you are uncertain, contact the drug manufacturer or look up the pharmacology data. Therapeutic drug monitoring is recommended for PMs to confirm that steady-state drug concentrations are within the therapeutic target interval.

UM- Increase dosage 2-5 fold depending on the number of duplications noted in the report. Success has also been achieved by concurrently administering another substrate or an inhibitor of CYP2D6.

IM - Start IMs at lowest efficacious dose and avoid multiple drug therapy that inhibits or activates through the same pathway.

Changes in metabolic capacity for an individual does not change the pharmacologic action of the medication. Therefore standard therapeutic drug concentration target intervals can be used to optimize dosage titration. The advantage of knowing the subject's genotype is in predicting the general dosage range for initiation and recognizing changes in time to achieve steady-state for interpretation of blood concentration monitoring.

Therapeutic drug monitoring is recommended in patients with metabolic variations. Keep in mind that subjects with metabolic deficiency will have decreased drug clearance and require additional time to achieve steady-state. In contrast, subjects with increased metabolic activity (UMs) have increased drug clearance and will achieve steady-state sooner than extensive metabolizers.

Cytochrome P-450 2C9 and 2C19

Phenotype prevalence is 3.7% PM, 38% IM for 2C9. Phenotype prevalence is 3% PM (for Asians 15-21%) for 2C19.

Therapy Modification

PM - Reduce dose to 20 - 60% of standard dosages.

IM - Start IM's at lowest efficacious dose, avoid multiple drug therapy that inhibits or activates through the same pathway.

Therapeutic drug monitoring in PM and IM subjects is highly recommended. Again standard measures of efficacy (INR for Warfarin or therapeutic target interval for Phenytoin, for example) can be applied to ensure optimal therapy.

Cytochrome P-450 1A2

CYP1A2 is primarily responsible for the metabolism of some important medications, including theophylline, clozapine, and caffeine. CYP1A2 is also involved in the metabolic activation of carcinogens from chemical toxins. There is considerable variation in 1A2 metabolic activity due to genetic factors, environmental factors, and drug-drug interactions. CYP1A2 is both inducible and can be inhibited, "turned on or off" by many medications and food-drug interactions. Fluoroquinolones, for example, are metabolized by and inhibit the

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enzyme CYP1A2. This can prevent the metabolism of concomitant medications such as theophylline and caffeine, causing excess central nervous system side effects and cardiac stimulation. Conversely, smoking may induce CYP1A2, resulting in enhanced metabolism of 1A2 substrates and the potential of sub-therapeutic response. The variation of the intensity of CYP1A2 activity could result in increased or decreased capacity to activate substrates.

Genetic polymorphisms in the CYP1A2 gene influence the magnitude of CYP1A2 induction. Two important polymorphisms that cause functional changes in enzymatic activity have been identified in the CYP1A2*1 allele. The CYP1A2*1C allele is the result of a single point mutation (-3860 G>A) in the 5'-flanking region of human CYP1A2 gene. This allele is associated with decreased CYP1A2 metabolic activity (measured in terms of the rate of caffeine metabolism) in comparison to the wild-type CYP1A2*1A allele. The CYP1A2*1F allele is the result of a single point mutation (-163 C>A) in intron 1, downstream of the first transcribed nucleotide of the human CYP1A2 gene. This allele has increased induction particularly in smokers (measured in terms of the rate of caffeine metabolism) in comparison to the wild-type CYP1A2*1A allele. The distribution of CYP1A2 genotypes at this nucleotide position (-163) is as follows: *1F/*1F (nucleotide sequence A/A) ~ 46 %; *1A/*1F (nucleotide sequence C/A) ~ 44%; and *1A/*1A (nucleotide sequence C/C) ~ 10%, indicating that high induction is the most common phenotype.

N-Acetyltransferase 2 (NAT2)

Phenotype prevalence is approximately 50% slow acetylators and 40% intermediate acetylators in the United States. Phenotype prevalence varies greatly by area, please refer to http://www.cdc.gov/genomics/hugenet/reviews/tables/n_acet_Tables.htm#t3 for prevalence in other areas.

Therapy Modification

Rapid acetylators (RA) represent the norm for metabolic capacity. Genotypes consistent with the RA phenotype include two active NAT2 alleles. In general rapid acetylators can be administered drugs which are substrates of the NAT2 enzyme following standard dosing practices.

Intermediate acetylators (IA) may require lower than average drug dosages for optimal therapeutic response. Genotypes consistent with the IA phenotype are those with one active and one inactive NAT2 allele.

Slow acetylators (SA) are at increased risk of drug-induced side effects due to diminished drug elimination or lack of therapeutic effect resulting from failure to generate the active form of the drug. Genotypes consistent with the SA phenotype are those with no active NAT2 alleles.

Key Terms

Substrates - If a drug is listed as a substrate of a pathway, that is the main pathway for metabolism.

Inhibitor - If a drug is listed as an inhibitor of a pathway, it reduces or blocks the ability of the pathway to metabolize the substrates.

Inducer - If a drug is listed as an inducer of a pathway, it will increase the ability of the pathway to metabolize the substrates.

Technical Bulletins

Technical Bulletins with more comprehensive information on Cytochrome P-450's CYP2D6, CYP2C9, CYP2C19 and CYP1A2 are available on our web site at <http://www.healthanddna.com/professional/testmenu.html#pgx>.

References

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2. Anderson T. et al. Drug-metabolizing enzymes: Evidence for clinical utility of pharmacogenetic tests. *Clinical Pharmacology & Therapeutics*, 78:6 559-581 (2005).

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3. De Leon, J. et al. Clinical Guidelines for Psychiatrists for the Use of Pharmacogenetic Testing for CYP450 2D6 and CYP450 2C19. *Psychosomatics* 47:1 75-85 (2006).

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