**What is the Cytochrome P450 System?**

When a drug is administered, it eventually finds its way out of the body. The time it takes for a drug level in the body to fall 50% is called its "half-life," often expressed as the term **t ½.** Some medications are excreted unchanged in the bowel (stools) or through the urinary tract however, most medications are excreted after being chemically changed or "metabolized" by enzymes in the body. When a drug is metabolized, it can be activated from a pro-drug to an active drug, changed from an active drug to an active metabolite, or deactivated. As an example of how drug metabolism works; the commonly used sedating antihistamine Atarax (Hydroxyzine) is metabolized by enzymes in the body and changed into a less sedating antihistamine Cetirizine (Zyrtec). After additional metabolism, Cetirizine is then changed into a more potent drug, Levocetirizine (Xyzal). Each of these metabolic intermediates has different pharmacologic properties and different half-lives.

Most medications are inactivated by a process called oxidation. The primary group of enzymes that performs this process is called the **Cytochrome P450 system**. Cytochrome P450 pathways are classified by their genetic DNA-sequence similarities and are assigned family number such as CYP1 or CYP2. Sub-variants in each family are further distinguished from each other by additional letters and numbers, for example (CYP1A1 and CYP1A2). Most drugs are metabolized in the liver however, other organs or cell types (Intestines, lungs, kidneys, and blood plasma) can play important roles in the deactivation or detoxification of drugs. About 80% of all drug that are cleared by the liver are metabolized by CYP1, 2 and 3 pathways. Drugs that interact with the CYP enzymes can interact in 3 possible ways: 1) a drug can be oxidized by the enzymes, and typically rendered inactive, 2) a drug could increase the activity of the CYP enzymes (Act as a pathway inducer), or 3) decrease the activity of a CYP enzyme (Act as a pathway Inhibitor). When two drugs that are detoxified by the same CYP pathway are administered concurrently, a drug that induces the P450 enzymes, increases the drug inactivation rates and lower effective drug levels. Conversely, a P450 pathway inhibitor can slow the metabolism of drugs and increase the levels of concurrently administered medications.

When a drug interaction lowers a medication's level, it may lose its clinical or therapeutic effectiveness. If a drug level is unexpectedly raised, it may become toxic or cause unexpected side-effects. In addition, if too many medications are given together that all utilize the same deactivation pathway, the P450 system can become overwhelmed, resulting in a prolongation of the time (t ½) medications remains active in the body. When drugs are not detoxified and excreted at the expected rate, and if the time between doses is not increased to compensate for this effect, drug levels in the body can rise and may cause toxic or adverse reactions.

Typically, if you use the same Pharmacy Distributor for **all** your medications, the Pharmacist's dispensing software automatically detects potential adverse interaction between your medications; based on their likely effect(s) on the function of the P450 enzymes and other known potential interactions. These incompatibility issues are typically ignored by the Pharmacists unless a very "serious" adverse interaction is identified. What the Pharmacist doesn't know is if you have a genetic variant of a P450 cytochrome that is either more active or less active than the "normal" gene that produces the most common and functional P450 enzyme type.

**How can my P450 genetics be used to influence the choice of Medications.**

The genes that are involved with the P450 system exist as multiple genetic variants or polymorphisms called "alleles". Each cytochrome P450 allelic variant metabolizes drugs at a different rate; some normally, some more rapidly, some slower and some not at all. Each person's ability to metabolize drugs is determined by the pairing of their 2 alleles for each of the P450 pathways (one gene allele is derived from the mother, the other from the father). Alleles are classified as "wild-type" (a normal functional P450 gene) or as ***abnormal*** genes. When 2 functional "normal" genes are inherited together, drugs will be metabolized at a "normal" rate. If one functional and one "slower" gene is inherited, an "intermediate rate" of drug metabolism would be expected. When two low functioning, genes are present, a very slow drug metabolism should be anticipated. Rarely, if two non-functional alleles are inherited, the metabolism of drugs normally inactivated by this specific P450 pathway might not occur at all.

Before the FDA approves a new drug, studies must be conducted to determine how the drug is either excreted or metabolized by the body. If the drug is metabolized (oxidized), the specific P450 pathway responsible is usually identified. Drug studies are typically conducted on large groups of participants but P450- genetic testing of participants for allele variations is not typically done. Logically, simply by chance, most participants in any drug study would have the most common and functional (wild-type) genetic variant of a P450 pathway enzyme. As a result, when a drug-metabolism study is reported to the FDA, the findings represent what would be expected to occur primarily in someone with the most common functional "normal" variant of a P450 cytochrome gene type.

Genetic testing can identify **your specific P450 genotype** for each of the parental allele controlling each unique P450 pathway. Since most P450 genetic variants have been functionally characterized as "normal, poorly effective, or non-functional", this information can be used to estimate how you would metabolize any medication that would be metabolized by a P-450 pathway. For example, an actual genetic profile is shown below (Table 1) with an explanation for how each of the paired alleles would be expected to affect drugs metabolized by the designated P450 pathways.

For the CYP2B6 pathway, both genes (Two allele #6 variants) produce "slower than normal" intermediate rate metabolizing enzymes and so an "intermediate" rate of drug metabolism (slower than normal) should be expected for any medications detoxified by this pathway.

For the CYP2C19 pathway, the allele #2 variant is a non-functional allele and the #17-variant has an increased activity. *It is uncertain if this gain of function variant (17) can fully compensate for the presence of the non-functional allele (2).

For the CYP1A2 pathway, the 1F variant allele can be affected by exposure to certain medications (P450-inducers) triggering an upregulation of its level of expression and activity. Consequently, if an inducer medication is being taken, and another medication is added that is also metabolized by the CYP1A2 pathway, the induced increase in CYP1A2 enzyme activity could increase the rate of drug metabolism and reduce the drug level of the medications, potentially rendering them clinically ineffective.

Table-1

## RESULTS REPORT: Pharmacokinetic Gene Variations; CYP450 Drug Metabolism

| GENE RESULT | THERAPEUTIC IMPLICATIONS | INTERACTION | CLINICAL IMPACT |
|---|---|---|---|
| CYP2B6<br>IM<br>*6/*6<br>[Intermediate activity] | *Intermediate metabolizer:↑ risk of elevated serum levels, drug interactions and ↓ production of active moieties*<br>• A dose adjustment or alternate therapy may be necessary |  | **Use caution** with medications metabolized by CYP2B6<br>*See Drug Interaction Summary for details* |
| CYP2C19<br>IM<br>*2/*17<br>[Intermediate activity] | *Intermediate metabolizer:↑ risk of elevated serum levels and drug interactions*<br>• A dose adjustment or alternate therapy may be necessary<br>• Intermediate activity is a provisional classification; the current literature indicates the *17 gain-of-function variant is not sufficient to fully compensate for a loss-of-function variation. This data, however, has not been consistently replicated |  | **Use caution** with medications metabolized by CYP2C19<br>*See Drug Interaction Summary for details* |
| CYP1A2<br>EM<br>*1A/*1F<br>[Normal activity and risk for induction **in the presence of inducers**] | *Variations in the CYP1A2 liver enzyme can result in altered drug metabolism and unexpected drug serum levels*<br>• This genotype confers normal activity<br>• This patient, however, **in the presence of inducers**, is *at risk for induction of CYP1A2* which may increase metabolism due to the presence of the *1F allele (see the Genecept Assay Report Interpretation Guide for full list of inducers) |  | There are no known gene-drug interactions for this genotype |
| CYP2C9<br>EM<br>*1/*1<br>[Normal activity] | *Variations in the CYP2C9 liver enzyme can result in altered drug metabolism and unexpected drug serum levels*<br>• This genotype confers normal activity |  | There are no known gene-drug interactions for this genotype |
| CYP2D6<br>EM<br>*2/*4<br>[Normal activity] | *Variations in the CYP2D6 liver enzyme can result in altered drug metabolism and unexpected drug serum levels*<br>• This genotype confers normal activity |  | There are no known gene-drug interactions for this genotype |
| CYP3A4<br>*1/*1<br>CYP3A5<br>*3/*3<br>[Normal activity] | *Variations in the CYP3A4/5 liver enzymes can result in altered drug metabolism and unexpected drug serum levels*<br>• This genotype confers normal activity<br>• CYP3A activity is determined by the sum activity of the CYP3A family of genes; in adults the most influential are CYP3A4 and 3A5 |  | There are no known gene-drug interactions for this genotype |

The genetic make-up (genotype) of the CYP2C9, CYP2D6 and CYP3A4 & 5 pathways all provide for "Normal" rates of drug metabolism.