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Cytochrome P450 Enzyme Genotyping: Optimizing Patient Care Through Pharmacogenetics

Each year more than 2 million Americans are hospitalized due to adverse drug reactions,[1] which lead to an estimated 100,000 deaths. While many clinical factors play a role in adverse drug reactions, research has demonstrated that genetic factors may profoundly influence a person's response to medications, including possible side effects. The study of the genetically determined individual response to drugs is called pharmacogenetics.

Pharmacogenetics

Simply defined, pharmacogenetics is an aspect of personalized medicine, whose goal is safer, more efficient, customized drug therapies based on an individual's unique DNA profile. Variations in a gene's DNA sequence, when present in at least 1% of a population, are called polymorphisms (less common variations are called mutations). Polymorphisms may result from a single nucleotide substitution, or the deletion or addition of nucleotides. These structural changes in a gene's DNA sequence may influence drug efficacy and side effects. Currently, much of the pharmacogenetic effort is focused on defining those genotypes that can explain why some patients do not respond to high doses of a medication, while others have side effects or toxic reactions at low doses of the same medication. Since cytochrome (CYP450) enzymes are responsible for metabolizing nearly half of all drugs on the market today, much effort has been directed at cataloging the P450 gene variants (polymorphisms) that cause individual variability in drug response.[2,3]

Cytochrome P450 Enzymes

The CYP450 enzymes are a group of at least 57 different proteins that are each coded by a different gene.[4] The CYP450 enzymes, also known as mixed function monooxygenases, are located in the microsomes of the endoplasmic reticulum in many cell types including the liver, small intestine, kidney, lung, brain, and skin. In mammals, the CYP450 enzymes are the primary catalysts for detoxification reactions that render water-insoluble molecules sufficiently water soluble to be excreted in the urine (see figure 1). Drugs, hormones, toxins, carcinogens, mutagens, environmental pollutants, and other xenobiotics are metabolized by the CYP450 enzymes.

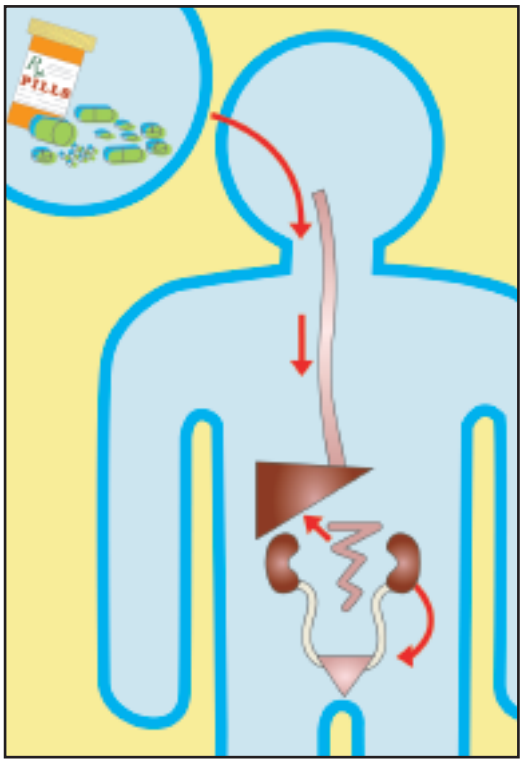

Figure 1. Drug metabolism pathway

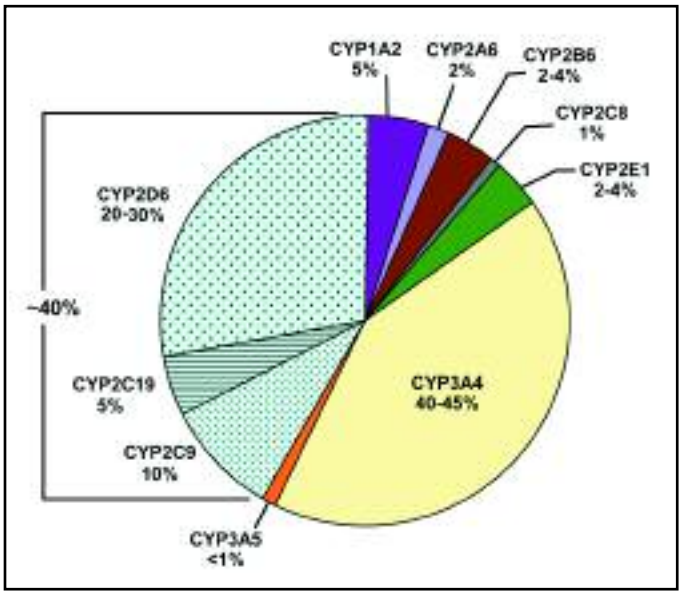

***Figure 2**. Primary CYP450 Drug-Metabolizing Enzymes and Relative Contribution to Known Drug Metabolism*[5]

In humans, the CYP450 families 1-3 are primarily involved in approximately 75% of oxidative Phase I-catalyzed drug metabolism (oxygenation, followed by hydroxylation, reduction, and hydrolysis). Most drug metabolism is performed by 10 key CYP450 enzymes (see Figure 2).[5] While gene variants have been identified for each of the key drug-metabolizing CYP enzymes, the functional importance and frequency of the variants differ. Several clinically relevant variants have been identified for the CYP2C9, CYP2C19, and CYP2D6 enzymes, which combined are responsible ~40% of CYP450-mediated drug metabolism.[5] Variants of these 3 enzymes result in abnormal drug metabolism (see Characterization of Metabolic Types). Conversely, variants of CYP3A4, which account for 45% of CYP450-mediated drug metabolism, are rare and have not been demonstrated to have adverse clinical effects.

Characterization of Metabolic Types

CYP450 enzyme-mediated drug metabolism displays wide interindividual variability. Several key polymorphisms may be associated with variability in the function of enzyme metabolism as compared to the normal gene structure. Most variants result in synthesis of enzymes that are diminished or devoid of catalytic activity. Alternatively, duplication gene variants result in increased metabolic activity (see Table 1).

Extensive Metabolizers (EM)
These individuals possess the normal genotype—referred to as "wild type" by molecular biologists—which is free of inactivating polymorphisms, deletions, or duplications. In Caucasian populations, EM is the most common genotype. Current drug dosing recommendations typically assume that the patient is an extensive metabolizer.

Poor Metabolizers (PM)
These individuals are homozygous for an inactivating polymorphism or compound heterozygous for 2 different inactivating polymorphisms. The severity of functional enzyme deficiencies varies among those with a PM genotype, though most lack a functional enzyme. Especially important for PM individuals is that they often do not receive any therapeutic benefit from drugs that are activated by CYP450 metabolism. Additionally, deficient enzyme function may result in an inability to clear certain medications, which may lead to toxicity and serious to sometimes life-threatening side effects.

Intermediate Metabolizers (IM)
These individuals have 1 normal allele and 1 allele with an inactivating polymorphism. Individuals with an IM genotype demonstrate a wide range of levels of enzyme activity. Some produce sufficient functional enzyme, while others do not. This group of metabolizers is particularly susceptible to abolishment of the residual functional CYP450 enzyme in response to inhibition by other drugs or metabolites. Thus, individuals with an IM genotype can develop a poor metabolizer phenotype in response to a "second hit" by the effects of drug inhibition or environmental factors.

Ultrarapid Metabolizers (UM)
These individuals have a duplication of a functional gene, resulting in ultrarapid metabolism. Presently, UM metabolizer genotypes have only been found for the CYP2D6 enzyme. Duplications from 3 to 13 copies of the *CYP2D6* gene have been reported and the rate of metabolism is often directly correlated to the number of copies present.[6] Individuals with a UM genotype may metabolize medications too quickly. Most often the drug is so rapidly cleared it does not reach therapeutic levels, and the therapeutic response is dramatically minimized or totally eliminated. This results in UM patients almost always being nonresponders to CYP2D6-metabolized antidepressant medications. Alternately, if a drug becomes effective only when it is metabolized, the UM patient may produce the metabolite more quickly than anticipated, resulting in toxicity and side effects.

Metabolic Type	Active Therapeutic Agent	
	Parent Drug	Metabolite
EM	• Normal metabolism • Optimal therapeutic benefit at normal drug dosages	• Normal metabolism • Optimal therapeutic benefit at normal drug dosages
IM	• Decreased drug metabolism • Vulnerable to metabolic inhibition due to drug interactions and other factors • Susceptible to toxic accumulation of parent drug and side effects at normal drug dosages	• Decreased drug metabolism, may result in inadequate transformation of parent drug into active metabolite • May experience reduced therapeutic benefit at normal drug dosages
PM	• Limited or no drug metabolism • Parent drug often accumulates to toxic levels • At high risk for serious adverse drug events at normal drug dosages	• Severely deficient or completely unable to transform parent drug into active metabolite • Little or no therapeutic benefit
UM	• Rapid drug metabolism • Circulating level of parent drug rapidly decreased below therapeutic threshold • Little or no therapeutic benefit at normal drug dosages	• Conversion of parent drug to metabolite occurs much more quickly than normal • The circulating metabolite is rapidly increased, often well above therapeutic levels • Toxicity and side effects may develop at normal drug dosages

Table 1: Metabolic Activity by Metabolic Type

Application of Pharmacogenetics: Genotyping for Drug Selection

Most psychotropic medications, including all common selective serotonin reuptake inhibitors (SSRIs), all common tricyclic antidepressants (TCAs), and some benzodiazepines and antipsychotics, are metabolized by the CYP450 enzymes. Mayo Medical Laboratories offers 3 CYP450 tests:

#83180 Cytochrome P450 2D6 Genotyping
#83652 Cytochrome P450 2C9 Genotyping
#83639 Cytochrome P450 2C19 Genotyping

These tests identify the patient's CYP450 metabolic genotype, which may affect treatment choices based on the patient's predicted response to various medications.

CYP2D6

The CYP2D6 enzyme is the most extensively characterized polymorphic drug-metabolizing enzyme. It is responsible for hydroxylation or dealkylation of at least 20% of all commonly prescribed drugs.[2] It participates in the hydroxylation or dealkylation of over 100 commonly prescribed drugs such as alpha-blockers, analgesics, anticonvulsants, antidepressants, antiemetics, antihypertensives, antiestrogens, antineoplastics, antipsychotics, antiretrovirals, antitussives, beta-andrenoceptor blockers, cardioactive drugs, H1 blockers, opioids, stimulants and sympathomimetics.[7]

Highly variable, with more than 160 variants identified to date, the *CYP2D6* gene is located on chromosome 22, where crossover events lead to duplication of this gene. *CYP2D6* poor metabolizers comprise 7% to 10% of Caucasian populations, 2% of African American populations, and 1% of Asian populations.[9] More than 15 million Americans are poor metabolizers of 2D6 substrates.

Case Example

CYP2D6 Genotypes and Codeine Metabolism

- The *CYP2D6* gene is responsible for metabolizing codeine.
- The metabolite of codeine, morphine, is responsible for the analgesic effect.
- EM process the codeine at a normal rate, and the codeine metabolite provides adequate analgesia.
- PM may not get adequate analgesia from codeine. Since they are deficient in functional 2D6 enzyme, they may be unable to metabolize codeine into its metabolite, which is responsible for pain relief.
- IM may have enough functional CYP2D6 enzyme to metabolize the codeine and experience adequate analgesia. However, if the deficiency is total or a secondary interaction further inhibits the enzyme levels, the IM may behave as a poor metabolizer.
- UM often process codeine very quickly, leading to much higher levels of the analgesic metabolite in their system, which may cause them to experience side effects including light-headedness, dizziness, and nausea.

#83180 Cytochrome P450 2D6 Genotyping is recommended for patients receiving medications for treatment of depression and other psychiatric disorders, since extensive interpretive expertise has been developed for this area. However, when specimens are submitted in conjunction with drugs used for other clinical purposes, the ordering physician will be consulted. Testing will only be performed if the drugs in question are indeed metabolized by CYP2D6 and the results will have pertinence to the clinical situation presented.

CYP2C19

The CYP2C19 enzyme is responsible for metabolizing various drugs used to treat ulcers, seizures, malaria, and anxiety. It is also partially responsible for metabolizing drugs such as beta-blockers and some antidepressants. #83639 Cytochrome P450 2C19 Genotyping is useful for identifying patients who are poor metabolizers or extensive metabolizers of drugs that are metabolized by CYP2C19.

More than 20 specific variants that result in functional enzyme deficiencies have been identified for the *CYP2C19* gene sequence located on chromosome 10. The most commonly detected variant alleles are *CYP2C19*2* and *CYP2C19*3*, and less frequently *CYP2C19*4* and *CYP2C19*8*. Poor metabolizers are found with the frequencies of 2% to 5% in Caucasians (85% are homozygous for the *CYP2C19*2* variant), 4% in African Americans, 13% to 23% in Asians (100% are heterozygous for the *CYP2C19*2* and *CYP2C19*3* variants), and 38% and 79% in Polynesians and Micronesians, respectively.[10]

CYP2C19 PM individuals may experience prolonged sedation and unconsciousness in response to diazepam. Of interest is the report that CYP2C19 PM individuals have a better chance of being cured of gastric ulcers and *Helicobacter pylori* infections with omeprazole therapy, due to the higher circulating blood levels of the drug.[10] Increased therapeutic doses of omeprazole may be required for EM and IM metabolizers.

CYP2C9

The CYP2C9 enzyme metabolizes a wide variety of drugs including warfarin (Coumadin), many nonsteroidal anti-inflammatory drugs (NSAIDs), fluoxetine, fluvastatin, oral hypoglycemic drugs, phenytoin, antiepileptics, angiotensin II blockers, and sulfonylurea antidiabetic drugs.

More than 27 variants have been discovered for the *CYP29C* gene located on chromosome 10. Unexpectedly, the homozygous *CYP2C9*2/*2* genotype produces individuals who are considered intermediate metabolizers, since this variant has sufficient residual activity. Approximately 3% of Caucasians are considered PM and 38% are considered IM.[11] CYP2C9 PMs are more likely to become hypoglycemic when taking usual doses of the glucose-lowering drugs glipizide and tolbutamide, and may exhibit ataxia and mental confusion when taking phenytoin. Approximately 33% of Americans have either the PM or the IM *CYP2C9* genotype, which renders them >2 times more likely to

suffer serious bleeding episodes on warfarin therapy. *CYP2C9* variants account for approximately 6% of the variation in warfarin metabolism, but recent evidence demonstrates that vitamin K epoxide reductase gene variants account for >25% of the variation of warfarin metabolism in patients.[12]

#83652 Cytochrome P450 2C9 Genotyping is useful to assess hypoglycemia with accepted dosing of oral hypoglycemic agents and sulfonylureas, to aid in determination of the correct dose of warfarin to administer, to assist in altering dosing of antiepileptic drugs, to investigate adverse drug responses to fluoxetine, and to elucidate reasons for idiosyncratic reactions to NSAIDs.[11,13-16]

Table 2 provides a listing of the allelic variants tested and their effect on enzyme activity. Table 3 provides a listing of drug substrates, inducers, and inhibitors for the CYP2C9, CYP2C19, and CYP2D6 enzymes. Substrates are drugs that are metabolized by the enzyme in question. Inducers are drugs that increase enzyme activity or synthesis. Inhibitors are drugs that either repair the enzyme activity or synthesis.

The information in Tables 2 and 3 is constantly undergoing revision, as new genotypes and interactive drugs are identified. Updated information about CYP450 alleles is maintained by the Human Cytochrome P450 (CYP) Allele Nomenclature Committee.[17] A table of CYP450 drug substrates, inducers, and inhibitors is maintained by David Flockhart, MD, PhD, at the University of Indiana.[18] If you have questions about specific drugs, please contact Mayo's Nucleotide Polymorphism Laboratory at 800-533-1710.

An additional benefit of the cytochrome P450 genotyping tests is that they can be performed without taking patients off their medications. Traditional biochemical phenotyping tests for CYP450 enzymes are conducted by giving the patient a test drug whose metabolism is exclusively dependent on the specific CYP450 enzyme of interest and measuring the ratio of unmetabolized drug to the metabolite found in serum or urine. This requires a drug-free patient, since many drugs and even herbal products can inhibit enzyme function. Genotyping enables testing without waiting days or weeks for drugs to clear from the patient's system.

Allele	Polymorphism	Effect of Polymorphism on Enzyme Activity
CYP2C19		
**1*	None (wild type)	EM (normal)
**2*	681 G>A	No activity
**3*	636 G>A	No activity
**4*	1 A>G	No activity
**5*	1297 C>T	No activity
**6*	395 G>A	No activity
**7*	IVS 5+2T>A	No activity
**8*	358 T>C	Severely decreased activity (70% to 90%)
CYP2C9		
**1*	None (wild type)	EM
**2*	430 C>T	Reduced activity
**3*	1075 A>C	Minimal activity
**4*	1076 T>C	Reduced activity
**5*	1080 C>G	Reduced activity
**6*	818 delA	No activity
CYP2D6		
**1*	None (wild type)	EM
**2*	2850 C>T	Decreased activity
**2A*	2850 C>T and -1584 C>G	Increased activity
**3*	2549 A>del	No activity
**4*	1846 G>A	No activity
**5*	Gene deletion	No activity
**6*	1707 T>del	No activity
**7*	2935 A>C	No activity
**8*	1758 G>T	No activity
**9*	2613 del AGA	Decreased activity
**10*	100 C>T	Decreased activity
**11*	883 G>C	No activity
**12*	124 G>A	No activity
**17*	1023 C>T	Decreased activity
Gene duplication		Variable

Table 2: List of Alleles Screened in *CYP450* Genotyping Tests available from Mayo Medical Laboratories

CYP2C9

Substrates

Angiotensin II Blockers:
irbesartan
losartan

Anticoagulants:
S-warfarin

Antidepressants:
amitriptyline
fluoxetine
R-norfluoxetine

NSAIDs:
celecoxib
diclofenac
ibuprofen
meloxicam
naproxen
piroxicam
suprofen

Oral Hypoglycemic/ Sulfonylurea Agents:
glimepiride
glipizide
glybenclamide
glyburide
nateglinide
rosiglitazone
tolbutamide

Others:
fluvastatin
phenytoin
rosuvastatin
sulfamethoxazole
tamoxifen
torsemide

Inhibitors

Drug	Degree of inhibition
fluvastatin	+++
sulfaphenazole	+++
isoniazid	++
sulfamethoxazole	++
amiodarone	+
fluconazole	+
fluvoxamine	+
lovastatin	+
phenylbutazone	+
probenicid	+
teniposide	+
desmethylsertraline	<+
paroxetine	<+
sertraline	<+
S-norfluoxetine	<+
zafirlukast	<+
ticlopidine	unknown

Inducers

phenobarbital
rifampin
secobarbital

CYP2C19

Antidepressants:
amitriptyline
citalopram
clomipramine
fluvoxamine
fluoxetine
imipramine
moclobemide

Antiepileptics:
diazepam
phenobarbitone
phenytoin
primidone
S-mephenytoin

Others:
carisoprodol
cyclo-phosphamide
hexobarbital
indomethacin
R-mephobarbital
nelfinavir
nilutamide
progesterone
proguanil
propranolol
teniposide
R-warfarin

Proton-pump inhibitors:
lansoprazole
omeprazole
pantoprazole
E3810

Drug	Degree of inhibition
fluvoxamine	+++
ketoconazole	+++
cimetidine	++
indomethacin	++
lansoprazole	++
omeprazole	++
probenicid	++
ticlopidine	++
fluoxetine	<+
modafinil	<+
topiramate	<+
chloramphenicol	unknown
felbamate	unknown
oxcarbazepine	unknown

carbamazepine
norethindrone
prednisone
rifampin
not pentobarbital

CYP2D6

Substrates

Antidepressants:
amitriptyline
clomipramine
desipramine
duloxetine
fluoxetine
fluvoxamine
imipramine
minaprine
nortriptyline
paroxetine
venlafaxine

Antipsychotics:
aripiprazole
chlorpromazine
haloperidol
perphenazine
risperidone
thioridazine

Beta-blockers:
carvedilol
S-metoprolol
propafenone
timolol

Cardiac/ Antihypertensives:
alprenolol
bufuralol
debrisoquine
diltiazem
disopyramide
encainide
flecainide
mexiletine
propafenone
propranolol

Chemotherapeutics:
tamoxifen

Opioids:
codeine
methadone

Others:
amphetamine
atomoxetine
chlorpheniramine
dexfenfluramine
dextromethorphan
felbamate
lidocaine
mephobarbital
metoclopramide
methoxyampheta-mine
ondansetron
oxycodone
perhexilene
phenacetin
phenformin
sparteine
tramadol

Degree of inhibition	
+++	strong
++	moderate
+	weak
<+	very weak

Inhibitors

Drug	Degree of inhibition
cimetidine	+++
cocaine	+++
fluoxetine	+++
paroxetine	+++
perphenazine	+++
quinidine	+++
tegaserod	+++
amiodarone	++
biperiden	++
celecoxib	++
citalopram	++
clomipramine	++
desethylamiodarone	++
desmethylcitalopram	++
duloxetine	++
escitalopram	++
halofantrine	++
hydroxyzine	++
levomepromazine	++
metoclopramide	++
methadone	++
moclobemide	++
ritonavir	++
sertraline	++
tripelennamide	++
buproprion	+
chlorpromazine	+
chlorpheniramine	+
desmethylsertraline	+
red-haloperidol	+
lomustine	+
diphenhydramine	<+
chloroquine	<+
doxorubicin	<+
terbinafine	<+
vinblastine	<+
vinorelbine	<+
clemastine	unknown
doxepin	unknown
histamine H1 receptor antagonists	unknown
indinavir	unknown
mibefradil	unknown
ranitidine	unknown
ticlopidine	unknown

Inducers

dexamethasone
rifampin

***Table 3*:** Drug Interaction Table

Using Genotype-Based Dosing Recommendations
Dosing of CYP450-metabolized drugs may require adjustment for individual patients. PM individuals may benefit from a reduced dosage. UM patients may benefit from increased doses. Patients with either UM- or PM-expressed genotypes also may benefit from conversion to other comparable drugs that are not primarily metabolized by the CYP450 enzyme variant they possess. Close attention should be paid to drugs with the narrowest therapeutic window,with especially heightened monitoring for drug-drug interactions. Recommendations for pharmacogenetics-based drug dosages for CYP450 genotypes and antidepressant and antipsychotic medications have been extensively reviewed by Kirchheiner et al.[19,20]

Complicating Factors for Assessing Drug Dosage Recommendations Based on Metabolic Genotypes
The CYP450 genotyping tests detect only the specified polymorphisms (Table 2); they do not detect all known polymorphisms that result in altered P450 enzyme activity. Absence of a detectable gene mutation or polymorphism does not rule out the possibility that a patient has a rare genotype that is not detected by these tests. Mutations in the primer binding regions can affect testing and, ultimately, the geno-typing results. Additionally, more than 1 enzyme may metabolize the same substrate. This would mean that the drug could be metabolized effectively by another functional enzyme, even if one CYP450 enzyme lacks functional activity.

Environmental factors, age, concomitant diseases, smoking habits, nutrition, gender, alcohol, caffeine, charbroiled food, grapefruit juice, air/water pollutants, and impaired hepatic or renal function can lead to decreased metabolism by various CYP450 enzymes.

Drug interactions prove to be another complicating factor when attempting to correlate CYP450 genotypes with metabolic phenotypes. Drugs or their metabolites can affect CYP450 enzymatic catalytic activity, which can lead to toxicity or decreased therapeutic benefit. SSRIs, some TCAs and other xenobiotics may reduce or increase P450 enzyme catalytic activity (Table 3).[15,21,22] Drug induction of a CYP450 enzyme takes place over time. As the CYP450 enzyme concentration is increased, the inducing drug is metabolized more quickly, as are other drugs metabolized by the same CYP450 enzyme. Drug inhibition of a CYP450 enzyme occurs with the first dose of an inhibiting drug and reaches maximum inhibition when the drug reaches a steady state (4-7 half-lives) level.

Consequently, due to 1 or a combination of factors including drug interactions, environmental and clinical factors, and lifestyle choices, a patient may require a dosing decrease/increase greater than predicted by genotype alone.

Selecting Patients for *CYP450* Genotype Testing
Genetic testing is a sensitive topic for many patients. Care must be used to adequately explain the need for testing and the utility of the results. Testing may be used to identify patients who are poor or ultrarapid metabolizers to aid in determination of correct drug selection and dosage. Testing also may be appropriate for the following categories of patients':

- Patients with a history of adverse drug reactions, excessive side effects, or acute toxicity.
- Drug-resistant patients.
- Patients who want to speed up the process of finding an effective antidepressant.

Health Care Economics

Adverse events from taking either too high or too low a dose of medication can range from minor to life threatening. Even minor adverse events can result in additional office visits, while more severe events can include hospitalization and death. Preliminary findings suggest that patients taking medications metabolized by the CYP2D6 enzyme, who were subsequently identified as having either the PM and UM genotypes, required on average an expenditure of $4000-$6000 more than for EM and IM groups.[2]

Genotyping only needs to be performed once, and that information can be utilized for guiding drug treatments for the patient's lifetime. Once the patient's genotype is known, physicians can proactively select those drugs that match the patient's metabolic type.

An additional benefit of the cytochrome P450 genotyping tests is that they can be performed without taking patients off their medications. Traditional biochemical phenotyping tests for CYP450 enzymes are conducted by giving the patient a test drug whose metabolism is exclusively dependent on the specific CYP450 enzyme of interest and measuring the ratio of unmetabolized drug to the metabolite found in serum or urine. This requires a drug-free patient, since many drugs and even herbal products can inhibit enzyme function. Genotyping enables testing without waiting days or weeks for drugs to clear from the patient's system.

Summary

In the rapidly advancing field of pharmacogenetics, genetic testing is allowing physicians to begin to accurately predict which patients will benefit most from certain medications. Conversely, genetic testing enables the physician to identify those patients who will benefit from closer scrutiny and altered treatment regimes. Efforts to identify and develop tests for additional genotypic polymorphisms and to identify additional medications affected by the cytochrome P450 enzymes are rapidly expanding what we know about P450 pharmacogenetics.

Mayo Medical Laboratories currently offers testing for *CYP2D6*, *CYP2C9*, and *CYP2C19*. Test results are provided in an interpretive report that includes assay information, genotype, and an interpretation indicating whether results are consistent with a PM, IM, EM, or UM phenotype. The report lists drugs known to affect metabolism by the CYP450 enzyme of interest. The reports are prepared by a group of clinical and laboratory specialists who provide expert consultative support. Watch for future announcements of additional CYP test offerings. If you have any questions about selecting the appropriate test for your patient, please contact Mayo Laboratory Inquiry at 800-533-1710.

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Test Updates

Alpha-1-Microglobulin Reporting Change

Previously reporting only the alpha-1-microglobulin level, #81036 Alpha-1-Microglobulin 24-Hour, Urine now also reports creatinine (mg/dL) and the ratio of alpha-1-microglobulin to creatinine (mg/g). No other aspect of the test will change.

Retinol Binding Protein Reporting Change

Previously reporting only the retinol binding protein level, #81783 Retinol Binding Protein 24-Hour, Urine now also reports creatinine (mg/dL) and the ratio of retinol binding protein to creatinine (mg/g). No other aspect of the test will change.

Surgical Pathology Consultation Expanded to Include Synovial Sarcoma Anomalies by FISH

A recurrent, tumor-specific translocation t(X;18)(p11.2;q11.2) is observed in approximately 90% of synovial sarcomas (SS). A single gene, *SYT*, has been implicated on 18q11.2, while 1 of 3 related genes, *SSX1*, *SSX2*, or infrequently *SSX*, is usually involved on Xp11.2. The ratio of *SYT-SSX1* to *SYT-SSX2* is close to 2:1 in the majority of studies. Detection of these transcripts by reverse transcriptase-polymerase chain reaction (RT-PCR) (#83361 Synovial Sarcoma By Reverse Transcriptase Polymerase Chain Reaction, Paraffin), which allows specific identification of *SYT-SSX1* or *SYT-SSX2*, has greatly facilitated the diagnosis of SS. Identification of the *SYT-SSX1* fusion is associated with an unfavorable outcome with significantly shorter overall survival when compared to the *SYT-SSX2* fusion. Unfortunately, RT-PCR results may be equivocal or falsely negative due to many reasons such as when the available RNA is of poor quality or if a rare translocation partner is present. In these cases, FISH testing can be used to identify 18q11.2 *SYT* gene rearrangements in these tumors, which supports the diagnosis of SS.

#86177 Synovial Sarcoma (SS) Anomalies at 18q11.2, FISH is only available as part of MML's #5439 Surgical Pathology Consultation, and will be performed under the direction of the reviewing Mayo pathologist as a follow-up test supporting the diagnosis of SS when RT-PCR results are equivocal or do not support the clinical picture. Specific questions can be directed to Mayo Laboratory Inquiry at 507-533-1710.

T Cell/CD4 Monitoring Options

Assessment of immunity and immune deficiencies are commonly evaluated by measuring lymphocyte functions and quantitating lymphocyte populations. Lymphocyte subpopulations can be categorized by surface membrane antigens and flow cytometry in order to identify and quantitate various cell types (eg, T-cell, B-cell, NK-cell). In these situations, #9336 T- and B-Cell Quantitation by Flow Cytometry is the best choice; results are reported as the percent of lymphocytes that are T (CD3+), T-helper (CD3+, CD4+), T-suppressor (CD3+, CD8+), natural killer (CD16+56, CD3-), and B-lymphocytes (CD19+), and the absolute number of each cell type per mL of blood. This assay requires 4 mL of EDTA whole blood.

For HIV-infected persons the US Public Health Service recommends monitoring CD4 levels every 3 to 6 months. After the initial assessment, however, a complete lymphocyte panel is not required. When patients do not require a full panel, physicians can utilize #84348 CD4 Count for Monitoring, Blood. This assay requires only 3 mL of EDTA whole blood and costs almost 50% less than performing a full panel. Results are reported as the percent of lymphocytes that are T (CD3+), T-helper (CD3+, CD4+), and T-suppressor (CD3+, CD8+), as well as the absolute number of each cell type per mL of blood (eg, the CD4 cell count). In most situations, patients with HIV can be appropriately followed utilizing #84348 CD4 Count for Monitoring, Blood.

2005 Education **Calendar**

Interactive Satellite Programs . . .

Alzheimer's: An Update on Treatment and Research
September 6, 2005
Presenter: *Ronald C. Petersen, MD, PhD*
Moderator: *Robert M. Kisabeth, MD*

Genomics & Proteomics – An Update
November 1, 2005
Presenter: *David B. Schowalter, MD, PhD*
Moderator: *Robert M. Kisabeth, MD*

Upcoming Education Conferences . . .

Quality Phlebotomy: Back to the Basics
September 27, 2005
Airport Marriott • Los Angeles, California

Practical Surgical Pathology
September 29-October 1, 2005
Mayo Clinic, Siebens Building • Rochester, Minnesota

Practical Spirometry
November 17-18, 2005
Mayo Clinic, Siebens Building • Rochester, Minnesota

Real-Time PCR for the Clinical Laboratory
November 17-18, 2005
Mayo Clinic, Siebens Building • Rochester, Minnesota

FOR MORE INFORMATION on these continuing medical education programs, please contact: Mayo Reference Services Education Department at 800-533-1710 or 507-284-3156. Visit us under "Education" at www.mayoreferenceservices.org

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