



Gualberto Ruaño, MD, and Bruce Bower, MD, of the Laboratory of Personalized Health stand in front of a DNA array representation used to evaluate drug safety and efficacy. Each column represents a patient and each row a gene polymorphism.

Personalized Drug Therapy and DNA-Guided Medicine at Hartford Hospital

BY GUALBERTO RUAÑO, MD, PHD,
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One of the promises of the Human Genome Project is individualization of patient care based on highly heterogeneous innate metabolic factors determined by DNA typing of gene polymorphisms. The practice of DNA-guided medicine requires the translation of such gene polymorphism into clinical decision support for personalized health care. Pharmacogenetics serves as the foundation for the most clinically advanced application of DNA-guided medicine.

Located at Hartford Hospital, the Laboratory of Personalized Health (LPH, Division of Genomas), performs clinical DNA typing for pharmacogenetic case referrals. Operational since October 2005, LPH has already diagnosed drug metabolism capacities for 500 patients

referred by physicians at Hartford Hospital and throughout Connecticut. LPH is licensed by the Connecticut Department of Health and certified by the Centers for Medicare and Medicaid Services as a high-complexity clinical molecular laboratory.

The hepatic cytochrome P450 (CYP450) isoenzymes CYP2D6, CYP2C9 and CYP2C19 metabolize and inactivate many drugs, including antidepressants, antipsychotics, anticoagulants and analgesics. They also metabolize selective pro-drugs into their active metabolites. These isoenzymes are highly polymorphic in gene sequence and protein structure. Their resultant variable biochemical properties substantially alter individual patient drug response. By means of DNA typing, the innate drug metabolism capacity of the patient can be predicted and diagnosed simply from a blood sample. LPH has analyzed the frequency of CYP450 polymorphisms in Hartford Hospital populations¹ and determined that ~50% of patients are carriers of a deficient or null polymorphism for CYP2D6, and ~25% for CYP2C9 or CYP2C19.

Many psychotropics—including selective serotonin reuptake inhibitors, atypical antipsychotics, tricyclic antidepressants and attention deficit hyperactivity disorder agents—are metabolized by the CYP450 isoenzymes. Inherited common variations in DNA result in extremes of enzymatic activity with resultant highly deficient or ultra-rapid drug metabolism. DNA typing is valuable in the diagnosis of patients refractive to psychotropic therapy or prone to recurrent side effects. In a case report from the Institute of Living, a patient with a six-year history of adverse effects to 18 psychotropics was diagnosed by DNA typing at LPH as profoundly deficient in drug metabolism

of CYP2D6, CYP2C9, and CYP2C19 genes². DNA typing is also relevant to the management of psychotropic prescription for highly vulnerable populations such as children and adolescent patients. Therapy can be directed to drugs whose primary metabolic pathways are least deficient or normal in an individual patient.

Warfarin (Coumadin[®]) is widely prescribed for management of atrial fibrillation, cardiac valve surgery, orthopedic procedures, pulmonary embolism and deep vein thrombosis. Yet warfarin management presents a clinical conundrum. There is a broad range of maintenance doses within the population to obtain therapeutic anticoagulation. The drug label carries a black box warning for bleeding, which is common despite periodic international normalized ratio monitoring. Warfarin is metabolized by the CYP2C9 isoenzyme and exerts its anticoagulant effect through inhibition of vitamin K epoxide reductase (VKOR), which reduces vitamin K for activation of various clotting factors. Patients who are carriers of both CYP2C9 and VKOR polymorphisms have a significantly higher rate of bleeding complications. New dosage guidelines are available from dosing algorithms now significantly enhanced with CYP2C9 and VKOR gene polymorphisms³. In August 2007, the FDA revised the drug label for Coumadin[®] to reflect this new gene-based prescription guidance.

Tamoxifen (Nolvadex[®]) and codeine are examples of pro-drug activation by the CYP2D6 isoenzyme. Tamoxifen is metabolized to the biologically active intracellular metabolite endoxifen. Breast cancer patients with deficient or null CYP2D6 polymorphisms experience less benefit from tamoxifen and have higher recurrence rates and deaths. Codeine is metabolized to its active metabolite morphine. If given standard codeine doses, patients deficient or null for CYP2D6 metabolism may not experience analgesia, while ultra-rapid metabolizers may experience apnea or even respiratory arrest.

Patients can be referred to LPH through the Clinical Laboratory Partners network throughout Connecticut. Currently, DNA typing for psychotropics, warfarin and tamoxifen is being reimbursed for clinically relevant cases. Multi-gene polymorphisms identifying patients at risk of statin-induced myopathy, glitazone-related edema, and psychotropic-induced metabolic syndrome are under development. Hartford Hospital is thus at the vanguard of DNA-guided medicine, with current clinical applications to personalize drug therapy and improve patient safety.

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References / further reading:

¹ Ruaño G, Makowski G, Windemuth A, Kocherla M, Weiss S, Goethe J.W., Bower B, Wu A.H.B., Thompson P.D. High carrier prevalence of deficient and null alleles of CYP2 genes in a major USA hospital: Implications for personalized drug safety. *Personalized Medicine*, 3: 131-137, 2006

² Ruaño G, Blair CL, Bower B, Windemuth A, Kocherla M, Aleman Y, Pearlson G, Goethe JW, Schwartz HI, Somatic Complications of Psychotropic Medications in a Patient with Multiple CYP2 Drug Metabolism Deficiencies. *Connecticut Medicine*, 71: 197-200, 2007

³ Ruaño G, Bower B. The Pharmacogenomics of Warfarin (Coumadin[®]) Administration. *Connecticut Medicine*, 70: 251-252, 2006

Current Gene Assays for DNA-Guided Management in Neuropsychiatry, Cardiology and Oncology

DRUGS	GENE ASSAYS*
Antidepressants, Antipsychotics	CYP2D6 + CYP2C9 + CYP2C19
Warfarin (Coumadin [®])	CYP2C9 + VKOR
Tamoxifen (Nolvadex [®]), Codeine	CYP2D6

*More information on DNA typing procedures at LPH is available at www.genomas.net/LPH.



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