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## Issues in Emerging Health Technologies

# CYP450 Genotyping for Determining Drug Metabolizer Status

### Summary

- ✓ **The AmpliChip CYP450 test (AmpliChip) is a drug metabolizing enzyme (DME) genotyping system that detects variations in CYP2D6 and CYP2C19 genes. The CYP2D6 and CYP2C19 enzymes metabolize many prescribed drugs (e.g., antidepressants, antipsychotics, and proton pump inhibitors). Variations in metabolism can lead to suboptimal therapeutic response or adverse drug reactions (ADRs).**
- ✓ **No published studies show that patient outcomes can be predicted or altered by knowledge of DME status in the absence of other confounding variables.**
- ✓ **Prospective studies are needed to assess the benefits and potential risks of this technology in guiding drug selection and dose adjustment. Until such studies are available, DME test results can only supplement other tools for therapeutic decision making, with routine monitoring by a physician.**

### The Technology

The AmpliChip CYP450 test (Roche Molecular Systems, Pleasanton CA) is a drug metabolizing enzyme (DME) genotyping system that detects genetic variations (polymorphisms) in two CYP450 genes, CYP2D6 and CYP2C19, using deoxyribonucleic acid (DNA) extracted from patients' blood. It is used with the GeneChip® System 3000Dx microarray platform developed by Affymetrix (Santa Clara CA). The test is conducted in a laboratory specializing in genetic analysis, and involves polymerase chain reaction (PCR) amplification of

selected DNA segments. The PCR products are fragmented, labelled, and hybridized to the microarray, then stained to produce fluorescent signal intensities that are captured by a laser scanner. The hybridization pattern is analyzed using software, to identify the CYP2D6 and CYP2C19 variations present. The resultant genotype and predicted phenotype are reported for each clinical sample.<sup>1</sup> The AmpliChip test queries for 31 polymorphisms and mutations, including gene deletions and duplications; and for CYP2D6, discerns which variation of the gene (allele) has been duplicated.<sup>1</sup> AmpliChip was developed as a diagnostic tool for physicians, to aid in the identification of the following CYP2D6 metabolizer phenotypes: poor metabolizer (PM), intermediate metabolizer (IM), extensive metabolizer (EM), or ultra-rapid metabolizer (UM); and of the CYP2C19 phenotypes (PM or EM).<sup>1</sup> The test is intended to help physicians with drug selection and individualization of drug therapy.

### Regulatory Status

AmpliChip is not yet licensed for use in Canada. It is considered to be a Class III medical device in Canada, and so it is subject to pre-market review (Maria Carballo, Therapeutic Products Directorate, Health Canada, Ottawa: personal communication, 2005 Dec 6). The US Food and Drug Administration (FDA) cleared AmpliChip in December 2004 for CYP2C19, and in January 2005 for CYP2D6.<sup>2</sup>

### Patient Group

The CYP450 enzymes form an isoenzyme superfamily that catalyze the oxidation of many drugs and chemicals.<sup>2</sup> The polymorphic frequency of the isoenzymes varies with racial background, although ethnicity alone may be a

poor predictor of genotype, because of the variability in a given group. Approximately 5% to 10% of Caucasians of European ancestry are reported to be PMs of CYP2D6, and up to 7% are UMs.<sup>3,4</sup> In Asian populations, the prevalence of PMs and UMs is low (<1%), but the frequency of IMs is high.<sup>3</sup> In some African populations, the rate of UMs is reported to be as much as 29%.<sup>3</sup> For CYP2C19, the PM phenotype is found in 2% to 6% of Caucasian, and in 18% to 23% of Asian populations.<sup>3,4</sup>

The CYP2D6 and CYP2C19 enzymes metabolize >80 drugs in clinical use.<sup>4</sup> Polymorphisms in these enzymes can lead to inter-patient differences in drug exposure from standard doses, leading to toxicity in PMs or subtherapeutic concentrations in UMs. For prodrugs, which require CYP450 metabolic activation to reach their active form, PMs may show no response, but UMs may experience adverse drug reactions (ADRs) because of the enhanced formation of biologically active or toxic metabolites. Drugs that are metabolized by CYP2D6 include antidepressants, antipsychotics, antiarrhythmics, beta-blockers, and narcotics; those that are metabolized by CYP2C19 include proton pump inhibitors, diazepam, select anticonvulsants, and anti-infectives.

Patients could benefit from DME testing, with the individualization of drug selection or dose. The clinical significance would be greatest when the incidence of the polymorphism is high (>10%), the drug has a narrow therapeutic range, and its metabolism is highly dependent on the affected enzyme.<sup>5</sup> The number of metabolic pathways is a consideration, because the metabolism of a drug that is highly dependent on CYP2D6 or CYP2C19 may be significantly affected by the DME phenotype, whereas drugs that are metabolized through several pathways may not be.

## Current Practice

The AmpliChip test is the first DME genotyping system that has been cleared by the US FDA for in vitro diagnostic applications. No utilization data are available, and no consensus guidelines address appropriate use, or identify

groups that are most likely to benefit from the technology. Drug selection and dose adjustment in patients with DME polymorphisms are largely determined through the clinical assessment of response. Consequences are prolonged time to optimal therapy and possibly serious ADRs in some patients who have polymorphisms.<sup>6</sup> One available option is to determine the phenotype of patients before the start of therapy, by using a probe drug known to be metabolized by the enzyme of interest.<sup>7</sup> The probe drug is administered to the patient, and the metabolic ratio (parent drug to metabolite concentration in blood or urine) is monitored. This method is time-consuming and inconvenient; it requires that the patient be free of drug at the time of testing; and it only provides descriptive information based on specific clinical conditions.<sup>6,8</sup> As a result, it is rarely applied in the clinical setting.

## The Evidence

Although studies have shown that AmpliChip accurately identifies CYP2D6 and CYP2C19 polymorphisms, no published studies have linked the use of AmpliChip to an improvement in patient outcomes.

In two identified studies, AmpliChip was used to test patients' DNA for CYP2D6 alleles. In a naturalistic setting, one study examined the associations between PMs of CYP2D6 and ADRs, and discontinuations because of ADRs. Included in the study were 325 patients who were stabilized on the antipsychotic drug risperidone, and 212 patients who discontinued risperidone.<sup>9</sup> All clinical ratings, assessments, and reasons for discontinuation were blinded to the results of the genetic tests. PMs were significantly more likely to have experienced moderate to marked ADRs [adjusted odds ratio (AOR) 3.4 (95% CI: 1.5; 8.0)]. Discontinuations because of ADRs were also significantly greater among PMs [AOR 6.0 (95% CI: 1.4; 25.4)].<sup>9</sup> The second study evaluated the prophylactic use of ondansetron (an antiemetic drug) in 250 patients to determine if UMs had an increased rate of postoperative nausea and vomiting.<sup>10</sup> When analyzed by genotype, the incidence of vomiting was statistically signifi-

cantly higher among UMs ( $p < 0.01$  versus all other groups). The incidence of nausea did not differ significantly between groups.<sup>10</sup>

Ideally, if genotyping is to be clinically useful, it must have a high predictive value (i.e., a PM phenotype would be highly predictive of an ADR, or an UM of poor response). In the risperidone study, PMs of CYP2D6 accounted for 16% (12 of 73) of patients with moderate to marked ADRs, and 9% (nine of 81) of patients who discontinued risperidone because of ADRs.<sup>9</sup> In the ondansetron study, <50% (five of 11) of UMs exhibited poor response (vomiting), and no significant differences were found between phenotypes in the incidence of nausea.<sup>10</sup> Despite showing associations, neither study demonstrated that patient outcomes can be predicted or changed by knowledge of DME status in the absence of other confounding variables. Rather, these studies show the complex nature of predicting drug response, and the potential pitfalls of focusing on one of many variables that predict patient response.

## Adverse Effects

The risks that are associated with DME genotyping systems are the incorrect identification of genotype (false-positive or false-negative results), or the improper interpretation of results.<sup>2</sup> Inaccurate or missing results because of instrument failure, data management, or software are also risks. Until studies that assess the benefits and potential risks of this technology in guiding drug selection and dose adjustment are conducted, it is unknown if, or how often, treatment decisions based on DME testing can lead to harm. It has been recommended that test results only be used to supplement other tools for therapeutic decision making, with routine monitoring by a physician.<sup>2</sup>

## Administration and Cost

A laboratory with staff who are trained in genetic analysis should be able to complete the test within eight hours of receiving a standard blood sample.<sup>1</sup> Presumably, the test would have to be done once per patient to generate results

that are relevant for a variety of drugs. Whether the information is relevant for a particular drug must be validated.<sup>6</sup> The ex-laboratory cost for one AmpliChip test is approximately US\$500.<sup>11</sup> Each AmpliChip microarray is used once and then discarded.<sup>1</sup> The cost of the Affymetrix GeneChip® System 3000Dx instrumentation is US\$219,000 (Teena Dean, Affymetrix, Santa Clara, CA: personal communication, 2005 Dec 20).

## Concurrent Developments

The AmpliChip CYP450 test is Roche's first licensed AmpliChip product. Work is underway on the development of AmpliChip microarrays for additional in vitro diagnostic applications.<sup>1</sup> Examples of other CYP450 tests intended for clinical application are the CodeLink™ Human P450 SNP Bioarray (GE Healthcare, US), DrugMet™ Genotyping Test (Jurilab Ltd., Finland), Tag-It™ Mutation Detection Kits (Tm Bioscience, Canada), and the Invader® CYP450 2D6 Analysis Panel (Third Wave Technologies Inc., US).<sup>6,12</sup> None of these tests are licensed in Canada or the US.

## Rate of Technology Diffusion

In the US, AmpliChip is initially being promoted to psychiatrists. The likely time of licensing in Canada is 2007. There are a number of clinical studies underway worldwide, but none are located in Canada (Tita Forrest, Roche Molecular Systems, Pleasanton, CA: personal communication, 2005 Dec 20). It is expected that widespread diffusion will be limited by cost, and the availability of laboratories with trained technicians and the required instrumentation systems. Not all drugs subject to CYP2D6 and CYP2C19 polymorphism will require testing, especially if the therapeutic range is wide or the ADRs are mild. Whether the information provided by the test is valuable for patient care must be assessed for each drug in the context of other factors that can confound metabolism (e.g., age, gender, environment, concomitant drugs, comorbid disease, smoking, liver or kidney function, and possibly multiple genes coding for a DME), and influence



response (e.g., other genetic polymorphisms affecting drug receptors).

## Implementation Issues

To offer the Roche AmpliChip CYP450 test, a laboratory would be required to buy the Affymetrix GeneChip® System 3000Dx. At this time, the AmpliChip CYP450 test is the only diagnostic test that requires this instrumentation.

Pharmacogenomic testing carries many social and ethical issues. “Personalized” drug therapy may improve patient outcomes, and facilitate the development of new drugs, but there is a potential for the inappropriate or unjustified use of this test. This could have cost implications. Concern has been expressed that genotype testing could emphasize fundamental differences between ethnic groups, or could disqualify patients from treatment or insurance coverage because of a pre-existing condition.<sup>13</sup> While there may be an incentive for industry to validate the testing of drugs under development or with patent protection, there is likely no incentive to validate off-patent drugs. These issues underscore the need to identify groups of patients who are most likely to benefit from DME genotyping. Guideline development and cost-effectiveness evaluation will be key factors in defining the appropriate use of the AmpliChip CYP450 test.

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CCOHTA appreciates comments from its reviewers.

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