

# AMPLICHIP<sup>®</sup> CYP450 TEST

## PRODUCT MONOGRAPH

### INTENDED USE

The Roche AmpliChip CYP450 test is intended to identify a patient's CYP2D6 and CYP2C19 genotype from genomic DNA extracted from a whole blood sample. Information about CYP2D6 and CYP2C19 genotype may be used as an aid to clinicians in determining therapeutic strategy and treatment dose for therapeutic that are metabolized by the CYP2D6 or CYP2C19 gene product.

### SUMMARY AND EXPLANATION OF THE TEST

Cytochrome P450 isoenzymes are a group of heme-containing enzymes involved in oxidative metabolism of a number of drug classes and xenobiotics. The P450 genes are polymorphic which has a functional significance for drug metabolism as certain allelic variants exhibit either altered activity or complete absence of enzymatic activity.<sup>1</sup> The isoenzymes encoded by the CYP2D6 and CYP2C19 genes are responsible for the metabolism of a large number of widely prescribed drugs.<sup>2</sup> The CYP2D6 gene, encoding for debrisoquine hydroxylase, has at least 70 allelic variants<sup>1</sup> resulting in four phenotypic types:

poor metabolizers with gene inactivation of both alleles,

intermediate metabolizers with one reduced activity allele and one null allele,

extensive metabolizers with at least one functional allele,

ultrarapid metabolizers with excess enzymatic activity due to multiple copies (3-13) of functional alleles from gene duplication.<sup>3,4,5</sup>

The CYP2C19 gene, encoding the enzyme S-mephenytoin hydroxylase, has two major variant alleles that result in enzyme deficiency.<sup>6</sup> Differences in drug metabolism due to CYP450 phenotype can impact plasma levels of both the active moiety (drug or drug metabolite) and toxic metabolites. Poor metabolizers treated with drugs that are

extensively metabolized by these isoenzymes are at increased risk for an excessive or prolonged therapeutic effect and for toxicity, while ultrarapid metabolizers may not achieve therapeutic plasma levels with standard dosing. In the case of prodrugs that require enzymatic action to become therapeutic, the opposite phenomenon occurs. In addition, some drugs and xenobiotics are inhibitors or inducers of the cytochrome P450 isoenzymes resulting in additional drug interactions. Besides polymorphisms, other factors can influence drug interactions via affecting expression of the CYP proteins, including age, gender, hormones, hepatic disease, inflammation, nutrition, pregnancy and environmental factors.<sup>7</sup>

The enzyme encoded by CYP2D6 metabolizes many antidepressants, antipsychotics, antiarrhythmics, opiates, antiemetics and beta-adrenergic receptor blocker drugs.<sup>1</sup> The distribution of functional, reduced function, and nonfunctional CYP2D6 alleles shows racial/ethnic differences.<sup>8,9</sup> Functional CYP2D6 alleles are predominant in European Caucasians, while reduced function alleles have a high frequency in Asian and African populations and their descendants. Nonfunctional alleles are present at the highest frequency in European Caucasians, while these genotypes are less commonly seen in Asians. The frequency of the ultrarapid metabolizer phenotype is highest in Saudi Arabian and Ethiopian populations.<sup>10</sup> The enzyme encoded by CYP2C19 metabolizes compounds from the classes of anticonvulsants, proton pump inhibitors, anticoagulants, benzodiazepines, and antimalarials.<sup>2</sup> The two most common allelic variants of CYP2C19 (\*2 and \*3) result in a nonfunctional enzyme. The frequency of poor metabolizers is highest in Asian populations (approximately 15-30%).<sup>6</sup> Due to the impact of these polymorphisms upon the pharmacokinetics of antidepressants and anti-psychotics, as well as the metabolism of active metabolites, distinct CYP2D6 and CYP2C19 genotype based dose recommendations have been proposed to improve patient outcomes.<sup>11,12</sup>

Identification of patient CYP2D6 and CYP2C19 genotypes can be predictive of drug metabolism enzyme activity. This information may help clinicians to individualize drug treatment by selection of the appropriate therapies. These measures may improve patient outcome by reducing adverse drug reactions and improving drug efficacy.

## CLINICAL VALIDITY

Individual differences in metabolic rates alter the expected relationship between the dose of a drug and its concentration in the blood or the length of time it stays in the blood. Therefore, a polymorphism in the CYP2D6 and CYP2C19 enzymes can lead to excessive or prolonged therapeutic effect or drug-related toxicity after administration of a “typical” dose by failing to clear a drug from the blood or by changing the pattern of metabolism to produce toxic metabolites. This is particularly true of drugs with a narrow therapeutic index. Adjustment of drug dosage could be beneficial based upon knowledge of these differences in metabolism, particularly for individuals possessing the poor and ultrarapid metabolizer phenotypes (because of the variability in the knowledge of clinical utility with specific drugs that are metabolized by the CYP2D6 and CYP2C19 enzymes, clinicians should use professional judgement in the interpretation and application of results from this assay). Table 1 lists some clinically relevant drugs that are known substrates of CYP2D6 and CYP2C19 enzymes.

**Table 1: Clinically Relevant Drug Substrates for Metabolism<sup>66</sup>**

CYP2D6			
Beta Blockers	Antidepressants	Antipsychotics	Others
Carvedilol	Amitriptyline	Haloperidol	Atomoxetine
Metoprolol	Clomipramine	Risperidone	Codeine
Propafenone	Desipramine	Thioridazine	Dextromethorphan
Timolo	Imipramine		Flecainide
	Paroxetine		Mexiletine
	Venlafaxine		Ondansetron
			Tamoxifen
			Tramadol
CYP2C19			
Proton Pump Inhibitors	Anti-epileptics	Antidepressants	Others
Omeprazole	Diazepam	Amitriptyline	Cyclophosphamide
Lansoprazole	Phenytoin	Clomipramine	Progesterone
Pantoprazole	Phenobarbitone		

## RESULTS

### Interpretation of Results

#### CYP2D6 Alleles Queried with the AmpliChip CYP450 Test

The combination of polymorphisms allows for a prediction of the enzymatic activity of the CYP2D6 allelic gene product.<sup>21</sup> In Table 2 nucleotide changes that define the allele are shown in bold font.

**Table 2: Predicted Enzymatic Activity for CYP2D6 Alleles**

Allele	Nucleotide	Predicted Enzyme Activity	Reference
*1	None	Normal	Marez et al, 1997 <sup>22</sup> Sachse et al, 1997 <sup>4</sup> Kimura et al, 1989 <sup>23</sup>
*2ABD	<b>-1584G</b> , 1039C>T, 1661G>C, <b>2850C&gt;T</b> , <b>4180G&gt;C</b>	Normal	Johansson et al, 1993 <sup>3</sup> Panserat et al, 1994 <sup>24</sup> Raimundo et al, 2000 <sup>25</sup> Marez et al, 1997 <sup>22</sup>
*3	<b>2549A del</b>	None	Kagimoto et al, 1990 <sup>26</sup> Marez et al, 1997 <sup>22</sup>
*4ABDJK	100C>T, 1039C>T, 1661G>C, <b>1846G&gt;A</b> , 2850C>T, 4180G>C	None	Sachse et al, 1997 <sup>4</sup> Marez et al, 1997 <sup>22</sup> Kagimoto et al, 1990 <sup>26</sup> Gough et al, 1990 <sup>27</sup> Hanioka et al, 1990 <sup>28</sup>
*5	<b>Entire CYP2D6 Gene deleted</b>	None	Gaedigk et al, 1991 <sup>29</sup> Steen et al, 1995 <sup>30</sup>
*6ABC	<b>1707Tdel</b> , 1976G>A, 4180G>C	None	Marez et al, 1997 <sup>22</sup> Evert et al, 1994 <sup>31</sup> Daly et al, 1995 <sup>32</sup> Saxena et al, 1994 <sup>33</sup>
*7	<b>A2935C</b>	None	Evert et al, 1994 <sup>31</sup>
*8	1661G>C, <b>1758G&gt;T</b> , 2850C>T, 4180G>C	None	Broly et al, 1995 <sup>34</sup>
*9	<b>2613-2615delAGA</b>	Reduced	Tyndale et al, 1991 <sup>35</sup> Broly & Meyer, 1993 <sup>36</sup>
*10AB	<b>100C&gt;T</b> , 1039C>T, 1661G>C, 4180G>C	Reduced	Yokota et al, 1993 <sup>37</sup> Johansson et al, 1994 <sup>38</sup>
*11	<b>883G&gt;C</b> , 1661G>C, 2850C>T, 4180G>C	None	Marez et al, 1995 <sup>39</sup>
*15	<b>T138ins</b>	None	Sachse et al, 1996 <sup>40</sup>

Allele	Nucleotide	Predicted Enzyme Activity	Reference
*17	<b>1023C&gt;T</b> , 1661G>C, <b>2850C&gt;T</b> , 4180G>C	None	Masimirembwa et al, 1996 <sup>41</sup> Oscarson et al, 1997 <sup>42</sup>
*19	1661G>C, <b>2539-2542delAACT</b> , 2850C>T, 4180G>C	None	Marez et al, 1997 <sup>22</sup>
*20	1661G>C, <b>1973insG</b> , 1978C>T, 1979T>C, 2850C>T, 4180G>C	None	Marez-Allorge et al, 1999 <sup>43</sup>
*29	<b>1659G&gt;A</b> , 1661G>C, 2850C>T, <b>3183G&gt;A</b> , 4180G>C	Reduced	Marez et al, 1997 <sup>22</sup>
*35	-1584C, <b>G31A</b> , 1661G>C, 2850C>T, 4180G>C	Normal	Marez et al, 1997 <sup>22</sup> Gaedigk et al, in press
*36	100C>T, 1039C>T, 1661G>C, 4180G>C, <b>gene conversion to CYP23T in exon 9</b>	Reduced	Wang, 1992 <sup>44</sup> Johansson et al, 1994 <sup>38</sup> Leathart et al, 1998 <sup>45</sup>
*40	<b>1023C&gt;T</b> , 1661G>C, <b>1863ins(TTT CGC CCC)2</b> ; 2850C>T, 4180G>C	None	Gaedigk et al, 2002a <sup>46</sup>
*41	<b>-1548C</b> , 1661G>C, <b>2850C&gt;T</b> , <b>4180G&gt;C</b>	Reduced	Raimundo et al., 2000 <sup>25</sup> Raimundo et al., 2004 <sup>47</sup>
*1XN	duplicate active *1 genes (n is not determined-range 2 -13)	Increased	Dahl et al, 1995 <sup>48</sup> Sachse et al, 1997 <sup>4</sup>
*2XN	duplicate active *2 genes (n is not determined-range 2 -13)	Increased	Johansson et al, 1993 <sup>3</sup> Dahl et al, 1995 <sup>48</sup>
*4XN	duplicate active *4 genes (n is not determined)	None	Lovlie et al, 1997 <sup>49</sup> Sachse et al, 1998 <sup>50</sup>
*10XN	duplicate partially active *10 genes (n is not determined)	Reduced	Garcia-Barceló et al., 2000 <sup>51</sup> Ji et al., 2002 <sup>52</sup> Mitsunaga et al., 2002 <sup>53</sup> Ishiguro et al., 2004 <sup>54</sup>
*17XN	duplicate partially active *17 genes (n is not determined)	Reduced	Cai et al., 2004 <sup>55</sup>
*35XN	duplicate active *35 genes (n is not determined)	Increased	Griese et al, 1998 <sup>56</sup>
*41XN	duplicate partially active *41 genes (n is not determined)	Reduced	Candiotti et al., 2004 <sup>57</sup>

An Allele Table and a Site and Call List are provided by the Data Analysis Software. The Site and Call List describes the polymorphism site identified by the nucleotide position and base change as well as the polymorphism call. The possible results listed for each call are:

<b>WT</b>	homozygous wildtype.
<b>HET</b>	heterozygote.
<b>MUT</b>	homozygous mutant.
<b>No Call</b>	no call made.
<b>Positive</b>	the indicated mutation case is present.
<b>Negative</b>	the indicated mutation case is not present.

*Note: Please refer to the User's Manual for the AmpliChip CYP450 Data Analysis Software Version 2.0 for a detailed description of the Allele Table, and Site and Call List.*

#### Predicted CYP450 2D6 Metabolic Activity

The combination of the activity of the enzymes encoded by the two CYP2D6 alleles determines the overall metabolic activity for an individual. These combinations are shown in Table 3. There are four phenotypic types: poor metabolizers, intermediate metabolizers, extensive metabolizers, and ultrarapid metabolizers. The predicted phenotypes, based on the genotype call for the CYP2D6 and CYP2C19 genes are provided by the Data Analysis Software.

**Table 3: Drug Metabolism Phenotypes Associated with CYP2D6 Allelic Variants Identified by the AmpliChip CYP450 Test**

Predicted phenotypes of the 2D6 genotypes detected by AmpliChip CYP450

Allele	1	2	3	4	5	6	7	8	9	10	11	15	17	19	20	29	35	36	40	41	1XN	2XN	4XN	10XN	17XN	35XN	41XN	
1	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	U	U	E	E	E	U	E	
2		E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	U	U	E	E	E	U	E	
3			P	P	P	P	P	P	I	I	P	P	I	P	P	I	E	I	P	I	E	E	P	I	I	E	I	
4				P	P	P	P	P	I	I	P	P	I	P	P	I	E	I	P	I	E	E	P	I	I	E	I	
5					P	P	P	P	I	I	P	P	I	P	P	I	E	I	P	I	E	E	P	I	I	E	I	
6						P	P	P	I	I	P	P	I	P	P	I	E	I	P	I	E	E	P	I	I	E	I	
7							P	P	I	I	P	P	I	P	P	I	E	I	P	I	E	E	P	I	I	E	I	
8								P	I	I	P	P	I	P	P	I	E	I	P	I	E	E	P	I	I	E	I	
9									I	I	I	I	I	I	I	I	E	I	I	I	E	E	I	I	I	E	I	
10										I	I	I	I	I	I	I	E	I	I	I	E	E	I	I	I	E	I	
11											P	P	I	P	P	I	E	I	P	I	E	E	P	I	I	E	I	
15												P	I	P	P	I	E	I	P	I	E	E	P	I	I	E	I	
17													I	I	I	I	E	I	I	I	E	E	I	I	I	E	I	
19														P	P	I	E	I	P	I	E	E	P	I	I	E	I	
20															P	I	E	I	P	I	E	E	P	I	I	E	I	
29																	I	E	I	I	I	E	E	I	I	I	E	I
35																	E	E	E	E	U	U	E	E	E	U	E	
36																		I	I	I	E	E	I	I	I	E	I	
40																			P	I	E	E	P	I	I	E	I	
41																				I	E	E	I	I	I	E	I	

Allele	1	2	3
1	E	E	E
2		P	P
3			P

E
I
P
U

## CYP2C19 Alleles queried with the AmpliChip CYP450 Test

The presence or absence of the particular polymorphisms listed below determines the CYP2C19 allele and predicts the likely enzymatic activity of the gene product.<sup>58</sup>

The nucleotide changes listed in bold font define the allele.

**Table 4: Predicted Enzymatic Activity for CYP2C19 Alleles**

Allele	Nucleotide Change	Predicted Enzyme Activity	Reference
*1	None	Normal	Romkes et al. 1991 <sup>59</sup> Richardson et al, 1997 <sup>60</sup> Blaisdell et al, 2002 <sup>61</sup>
*2	<b>681G&gt;A</b>	None	de Morais et al, 1994a <sup>62</sup> Ibeanu et al, 1998b <sup>63</sup>
*3	<b>636G&gt;A</b>	None	de Morais et al, 1994b <sup>64</sup>

## Predicted CYP450 2C19 Metabolic Activity

The combination of the activity of the enzymes encoded by the two CYP2C19 alleles determines the overall metabolic activity for an individual. There are two phenotypic types: poor metabolizers and extensive metabolizers.

Allele	1	2	3
1	E	E	E
2		P	P
3			P

E	Extensive
P	Poor

## Geographic Distribution of Allele Frequencies

Polymorphisms of the CYP2D6 and CYP2C19 genes are unequally distributed among people of different geographical origins, with some polymorphisms and alleles found virtually in only one racial population. Approximately 7% of

Caucasians are CYP2D6 poor metabolizers, whereas only about 1-2% of Asian and 2-4% of African-American populations are in that same category.<sup>4,9</sup> However, high prevalence of several reduced activity alleles such as the CYP2D6\*10 allele in Asians (50% allele frequency), or the CYP2D6\*17 and CYP2D6\*29 alleles (approximately 30% each) in certain African populations, lead to a higher percentage of intermediate metabolizers with low enzyme activity. Although the extreme activities of the poor and ultrarapid metabolizer phenotypes have the greatest potential effect on individual drug response, intermediate metabolizers have also been shown to respond differently to certain drugs.<sup>65</sup> In contrast, approximately 29% of Ethiopians, 10% of Southern Europeans, and 1-2% of Northern Europeans are ultrarapid metabolizers, having inherited CYP2D6 gene duplications.<sup>9</sup>

The vast majority of poor CYP2C19 metabolizers are accounted for by the two common CYP2C19\*2 and CYP2C19\*3 alleles. Each of these null alleles is caused by a single nucleotide polymorphism that either causes a splice site defect or a stop codon. These two alleles are quite common among Asian populations where approximately 13-23% exhibit the poor metabolizer phenotype.<sup>6</sup> The CYP2C19 poor metabolizer phenotype is present in about 3-5% of Caucasian and African-American populations.<sup>6</sup>

Estimates of CYP2D6 and CYP2C19 allele frequencies in diverse populations are listed in Table 5 and Table 6.

**Table 5: Geographic Differences in CYP2D6 Allelic Frequencies<sup>9</sup>**

Allele	Predicted Enzymatic Activity	Japan	China	Caucasian EU	Caucasian US	Black American	Black African	Amerindian	Saudi Arabia	Turkey
*1	Normal	42-43%	23%	33-37%	37-40%	29-34%	28-56%	66%	*	37%
*2	Normal	9-13%	20%	22-33%	26-34%	20-27%	11-45%	19%	*	35%
*3	None	*	1%	1-4%	<2%	<1%	<1%	0	*	0
*4	None	<1%	0-1%	12-23%	18-23%	7-9%	1-7%	4%	4%	11%
*5	None	5-6%	6%	2-7%	2-4%	6-7%	1-6%	4%	<1%	15%
*6	None	*	*	<2%	1%	<1%	0	1%	*	7%
*9	Reduced	*	*	0-3%	2-3%	<1%	0	0	*	<1%
*10	Reduced	39-41%	50-70%	1-2%	4-8%	3-8%	3-9%	1-17%	<1%	6%
*17	Reduced	*	*	<1%	*	15-26%	9-34%	*	<1%	<1%
*41	Reduced	*	*	20%	*	*	*	*	*	*
*1xN	Increased	<1%	*	<1%	<1%	1%	3%	*	*	<1%
*2xN	Increased	<1%	1%	<2%	<1%	1%	3%	*	10%	<1%
*4xN	None	*	*	<1%	<1%	2%	1%	*	*	<1%

*Note: Percentages represent ranges of allelic frequencies reported in published studies.*

*\*No published data available*

**Table 6: Geographic Differences in CYP2C19 Allelic Frequencies<sup>6</sup>**

Allele	Predicted Enzymatic Activity	Chinese	Black	Caucasian
*1	Normal	65%	18%	84%
*2	None	30%	17%	15%
*3	None	5%	<1%	<1%

## PROCEDURAL LIMITATIONS

1. Some rare CYP450 alleles are not reported by the AmpliChip CYP450 Test.

These alleles are listed below:

CYP450	Alleles Not Reported by AmpliChip CYP450 Test
CYP2C19	4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16
CYP2D6	12, 13, 14, 16, 18, 21, 22, 23, 24, 25, 26, 27, 28, 30, 31, 32, 33, 34, 37, 38, 39, 42, 43, 44, 45, 46

2. New CYP450 alleles not identified at the time of release of AmpliChip CYP450 Data Analysis Software version 2.0 will not be correctly detected by the AmpliChip CYP450 Test. Most likely, a “No Call” result will be obtained for the relevant CYP450 gene.
3. Samples with CYP2C19 \*2/\*10 genotype may be miscalled by the AmpliChip CYP450 Test as CYP2C19 \*2/\*2 genotype. The expected phenotype of both of these genotypes is poor metabolizer.<sup>61</sup>

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