Supplemental Material

Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for cytochrome P450-2C19 (*CYP2C19*) genotype and clopidogrel therapy: 2013 Update

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CPIC Updates
Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines are published in full on the PharmGKB website (www.pharmgkb.org). Relevant information will be periodically reviewed and updated guidelines will be published online.

CPIC Updates in Supplement v2.1:

- **Updated literature review from February 2011 to February 2013.**
- **Updated *CYP2C19* genetic testing options and availability.**
- **New section on *CYP2C19* sequencing and novel variants.**
- **New section on candidate genes.**
- **New section on who could be considered for *CYP2C19* genotyping.**
- **Updated data linking *CYP2C19* genotype to phenotype.**

Literature Review

The PubMed database (NCBI) was searched using the keywords (CYP2C19 OR cytochrome P450-2C19) AND (clopidogrel) from 1966 to January 2013. Key publications of clinical pharmacogenetic studies on clopidogrel response include: (1-10). For additional reviews and consensus statements, see references: (11-20). For additional information on clopidogrel pharmacogenetics, see PharmGKB: http://www.pharmgkb.org/clinical/clopidogrel.jsp.

To construct a *CYP2C19* minor allele frequency table based on ethnicity, the PubMed® database (1966 to January 2011) and Ovid MEDLINE (1950 to January 2011) were searched using the following criteria: ((CYP2C19 or 2C19) AND (genotype OR allele OR frequency OR minor allele OR variant OR ethnic OR race OR racial OR ethnicity)) with filter limits set to retrieve "full-text" and "English" literature. Studies were considered for inclusion if: (1) the ethnicity of the population was clearly indicated; (2) either allele frequencies or alleles for *CYP2C19* genotypes were reported; (3) the method by which *CYP2C19* was genotyped appeared reliable; (4) the sample population consisted of at least 50 individuals; and (5) the study represented publication of novel data (no reviews or meta-analyses). In instances where genotype data from large cohorts of ethnically-diverse individuals were reported, without respect to ethnicity, studies were only considered if one ethnicity was ≥95% of the majority.

The combined analysis grouped subpopulations based on the Human Genome Diversity Project-Centre Etude Polymorphism Humain (HGDP-CEPH) (21, 22) and included 7,970 Africans, 7,920 Americans, 36,030 East Asians, 121,808 Europeans, 2,140 Middle Easterns, 13,742 Oceanians, and 7,248 South/Central Asians.

GENE: CYP2C19

A gene summary on *CYP2C19* has recently been published (23) and is available online at PharmGKB: http://www.pharmgkb.org/gene/PA124#tabview=tab3&subtab=31.

Genetic Test Interpretation

The haplotype, or star (*) allele name, is determined by the combination of single nucleotide polymorphisms (SNPs) that are interrogated in the genotyping analysis. Each star (*) allele is defined by a specific functional SNP or combination of SNP genotypes. For example, the *CYP2C19*2* haplotype is defined by the c.681G>A SNP that results in aberrant gene splicing; however, sub-alleles of **2* have been identified that harbor additional SNPs with limited or no added functional consequence (e.g., *CYP2C19*2A*, **2B*, **2C*, and **2D*; see http://www.cypalleles.ki.se/cyp2c19.htm). Thus, only analyzing the defining SNP (**2* in this case) is usually sufficient to determine a *CYP2C19* haplotype. The major nucleotide variants that constitute the most commonly tested haplotypes or star (*) alleles for *CYP2C19*, their respective RefSNP accession ID numbers (http://www.ncbi.nlm.nih.gov/snp/), and their effect on the CYP2C19 protein are summarized in **Supplemental Table S1**. The functional consequences of these variant alleles on CYP2C19 enzymatic activity are summarized in **Supplemental Table S2** and their multi-ethnic frequencies are listed in **Supplemental Tables S3** and **S4**.

CYP2C19 genotyping results are reported as a diplotype, which includes one maternal and one paternal star (*) allele (e.g., **1/*2*). Notably, one of the inherent limitations in a commercial genotyping test is that rare or previously undiscovered variants will not typically be included in targeted *CYP2C19* testing panels and the wild-type *CYP2C19*1* allele is, therefore, assigned in the absence of detected variant alleles. As a result, a potentially function-altering novel or rare *CYP2C19* mutation not included in a commercial genotyping panel would be incorrectly defined as *CYP2C19*1*. Fortunately, these variant alleles are rare in the general population (although the **3* loss-of-function allele is prevalent in Asians; **Supplemental Tables S3** and **S4**). Additional predicted metabolizer phenotypes based on *CYP2C19* genotype combinations and their average frequencies are summarized in **Supplemental Table S5**.

Available Genetic Test Options

Commercially available genetic testing options change over time and a number of different platforms are currently available for *CYP2C19* genotyping, some of which are approved by the U.S. Food and Drug Administration (FDA). In addition, some Clinical Laboratory Improvement Amendments (CLIA)-certified clinical laboratories perform *CYP2C19* testing using analyte-specific reagents as in-house validated Laboratory Developed Tests (LDTs). Consequently, different clinical laboratories may have different variant alleles included in their *CYP2C19* testing panels, which can lead to discrepant results between methodologies (see above, **Genetic Test Interpretation**).

At the time of this writing, three *CYP2C19* genotyping assays have been approved as *in vitro* diagnostic (IVD) tests by the U.S. FDA:

1. AmpliChip® CYP450 Test (Roche Molecular Systems, Inc., Pleasanton, CA)
2. Infiniti® CYP2C19 Assay (AutoGenomics, Inc., Vista, CA)
3. Verigene® CYP2C19 Test (Nanosphere, Inc., Northbrook, IL)

The AmpliChip® CYP450 Test interrogates *CYP2C19*2* and **3* (in addition to cytochrome P450-2D6 (*CYP2D6*) variant alleles). Both the Infiniti® CYP2C19 Assay and the Verigene® CYP2C19 Test (24, 25) interrogate *CYP2C19*2*, **3*, and **17*. AutoGenomics, Inc., also offers the expanded Infiniti® CYP450 2C19+ Assay that interrogates *CYP2C19*2*, **3*, **4*, **5*, **6*, **7*, **8*, **9*, **10* and **17*, which is not currently FDA-approved.

Other commercial *CYP2C19* platforms not currently FDA-approved include the xTAG™ CYP2C19 Kit from Luminex Molecular Diagnostics (Toronto, ON, Canada) that interrogates *CYP2C19*2*, **3*, **4*, **5*, **6*, **7* and **8*, the eSensor® 2C19 Test from GenMark Diagnostics, Inc. (Carlsbad, CA) that interrogates *CYP2C19*2*, **3*, **4*, **5*, **6*, **7*, **8*, **9*, **10*, **13* and **17* (26), and the iPLEX® ADME CYP2C19 Panel from Sequenom, Inc (San Diego, CA) that interrogates *CYP2C19*2 - *28*. Additionally, a rapid point-of-care assay has recently been reported that can genotype *CYP2C19*2* directly from a buccal swab in ~1 hour (Spartan Biosciences, Ottawa, ON, Canada) (27).

In addition to commercial assays, other *CYP2C19* LDTs have been reported. Some of which involve real-time PCR allelic-discrimination (TaqMan, Applied Biosystems, Foster City, CA) (5, 28-30), oligonucleotide ligation (SNPlex, Applied Biosystems, Foster City, CA) (5), matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (31), and restriction fragment length polymorphism (RFLP) analyses (1, 32, 33). Pharmacogenomic genotyping panels that include *CYP2C19* are also commercially available, including the Affymetrix DMET™ Plus Panel Kit (Affymetrix, Santa Clara, CA) (2) and the Illumina® VeraCode ADME Core Panel (Illumina, Inc., San Diego, CA). Any clinical genetics or molecular pathology laboratory using any of these assays are still required to implement these tests using established CLIA standards and guidelines.

The 2012 American Medical Association (AMA) Current Procedural Terminology (CPT) procedure code for *CYP2C19* testing is 81225. However, given the number of different molecular assays available to interrogate *CYP2C19*, some laboratories still may use analyte CPT codes for *CYP2C19* testing. It is the responsibility of the service provider to determine proper coding. Insurance provider coverage for *CYP2C19* testing is possible; however, when this is a concern, the insurance provider should be contacted prior to pursuing *CYP2C19* genotyping.

Several CLIA-certified academic and commercial clinical laboratories offer *CYP2C19* testing. In addition to inquiring directly to a specific laboratory regarding test availability and specimen requirements, a voluntary listing of testing providers and related genetic test information is publically available through the Genetic Testing Registry (GTR) of the National Institutes of Health (NIH): http://www.ncbi.nlm.nih.gov/gtr/.

CYP2C19 Sequencing and Novel Variants

In addition to targeted genotyping for *CYP2C19* variant alleles, clinical laboratories may perform

full-gene or selected exon *CYP2C19* sequencing. Moreover, emerging clinical genomics programs that perform whole-exome/genome next-generation DNA sequencing are increasingly being deployed across academic medical centers and commercial laboratories and some centers are performing next-generation sequencing with focused pharmacogenomic gene panels (including *CYP2C19*) for both research and clinical use. All of these sequencing programs would capture the common *CYP2C19* variants (e.g., **2*, **3*) but will also identify both rare (e.g., **4* - **8*) and novel *CYP2C19* variant alleles that have untested clinical significance with respect to clopidogrel response.

Different clinical laboratories can interpret identified sequence variants using independent criteria; however, consensus nomenclature supported by the American College of Medical Genetics and Genomics (ACMG) (34) includes five categories for identified sequence variants: pathogenic, likely pathogenic, unknown significance, likely benign, and benign. It is the responsibility of the board-certified clinical geneticists at each laboratory to report and classify any novel *CYP2C19* alleles in this testing scenario and to provide an interpretation as to the rationale behind their classification. Although it is challenging to infer any association with clopidogrel response in the context of a novel *CYP2C19* sequence variant, 'pathogenic' and 'likely pathogenic' variants may act biologically consistent with other common loss-of-function alleles (e.g., **2*, **3*) as these are variants that typically result in an upstream polypeptide frame-shift, premature or mutated stop codon, or canonical splice site mutation. Novel *CYP2C19* variants classified as 'unknown significance' (e.g., missense alterations, in-frame insertions/deletions, nonconserved nucleotide substitutions) or 'likely benign' should not be assumed to mimic the biological consequences of known *CYP2C19* loss-of-function alleles (e.g., **2*, **3*) and their established roles in clopidogrel response variability.

Of note, previously identified, but rare, *CYP2C19* alleles characterized by missense alterations (e.g., **9* - **26*) have been subjected to PolyPhen-2 and Sorting Tolerant From Intolerant (SIFT) algorithm analyses to computationally predict their effect on protein function (23). Although not a substitute for actual *in vitro* or *in vivo* enzyme activity analyses, these data can provide a basis for potential variant interpretation and consequences of these sequence alterations on CYP2C19 enzyme function.

Other Considerations and Genes

The defining polymorphisms of *CYP2C19*2* and **17* are c.681G>A and c.-806C>T, respectively. There is linkage disequilibrium (LD) between c.681G and c.-806T (e.g., |D'|=1.0 and r^2=0.064 in CEU HapMap sample; |D'|=1.0 and r^2=0.065 in YRI HapMap sample; and |D'|=1.0 and r^2=0.074 in CHB HapMap sample). This means that the less common **17* variant (c.-806T) always tracks on the same allele with the more common c.681G. This complicates any interpretation of whether these two variants act independently of one another, and published articles argue both for (29, 35) and against (15, 36, 37) this point. Additional literature and conflicting evidence for a role of *CYP2C19*17* in clopidogrel response (including bleeding risk) are summarized in **Supplemental Table S6**.

In addition, the rare *CYP2C19*4* (c.1A>G) loss-of-function allele has recently been identified in LD with **17* (c.-806C>T) in certain ethnic subpopulations and this haplotype is designated

*CYP2C19*4B* (38). Consequently, when genotyping **17* and not **4*, it is possible that some identified **17* carriers will actually be **4B* carriers (a loss-of-function allele), particularly if they are of Ashkenazi Jewish ancestry.

CYP2C19 loss-of-function alleles do not account for all of the variability in clopidogrel response. Other genetic variants with smaller effects and rare variants likely also influence the response to clopidogrel. Some candidate gene and clinical studies have implicated variants in other genes (e.g., *ABCB1* (5, 8), *CES1* (39), *CYP2B6* (2), *CYP2C9* (32, 40, 41), *CYP3A4* (42), *P2RY12* (43, 44), and *PON1* (45)) associated with clopidogrel response; however, these studies have not all been adequately replicated to justify the clinical utility of these genes and variants. In particular, the reported association between *PON1* and clopidogrel pharmacokinetics, pharmacodynamics and clinical outcomes has been refuted by a number of recent reports (46-53) (see below).

ABCB1

The multidrug resistance protein 1 (MDR1), also known as P-glycoprotein 1 (P-gp), is an ATP-binding cassette (ABC) efflux transporter encoded by *ABCB1* that is involved in the intestinal absorption of clopidogrel. Interindividual variability in *ABCB1* expression and P-gp function is observed and the common synonymous c.3435C>T (rs1045642) allele has been widely studied in association with clopidogrel and other drugs. An early study on the impact of *ABCB1* on clopidogrel absorption reported that *in vitro* clopidogrel efflux clearance was driven by P-gp and that c.3435T homozygotes had lower plasma concentrations of clopidogrel and its active metabolite compared to c.3435C carriers, presumably due to higher *ABCB1* expression associated with the T/T genotype (54). Additional studies have since reported an association between c.3435C>T and increased platelet reactivity (55) and an increased risk of cardiovascular events during clopidogrel treatment (5, 8, 49), while other studies could not support such associations (56-58) or found an opposite effect (9). A meta-analysis examined the risk of high platelet reactivity and poor clinical outcomes with *ABCB1* c.3435C>T carriage during treatment with clopidogrel among coronary artery disease patients and concluded that there was no significant association between c.3435C>T and high platelet reactivity (59). Additionally, long-term risk for major adverse cardiovascular events (MACE), incidence of stent thrombosis, myocardial infarction, or ischemic stroke rate was also not associated with *ABCB1* c.3435C>T. However, c.3435C>T was associated with the risk of long-term MACE among patients treated with a 300 mg clopidogrel loading dose, and c.3435T homozygotes had a lower bleeding outcome rate than c.3435C homozygotes (59). The *ABCB1* c.3435C>T allele was also recently associated with adverse cardiovascular events (in combination with *CYP2C19*2*) among clopidogrel-treated acute coronary syndrome patients undergoing percutaneous coronary intervention (ACS/PCI) (60). Given the conflicting results surrounding the c.3435C>T allele, further studies are warranted to better understand the relationship between *ABCB1* and clinical outcomes following clopidogrel treatment.

CES1

Carboxylesterase 1 (CES1) catalyzes the transformation of clopidogrel, 2-oxo-clopidogrel, and the thiol metabolites into inactive carboxylate metabolites (45, 61). Two nonsynonymous polymorphisms have been identified, rs71647871 (c.428G>A; G143E) and rs71647872 (D260fs), which alter CES1 enzyme activity and result in dramatically decreased catalytic activity (62). The minor allele frequency of G143E is estimated to range from ~1-4% in white,

black and Hispanic populations, while the D260fs allele is considered rare (62). Given that the majority of the clopidogrel prodrug (85%) is inactivated via CES1-mediated hydrolysis (63), reduced function *CES1* alleles potentially could influence clopidogrel metabolism. Importantly, *in vitro* studies of CES1 enzymatic activity have suggested that the G143E and D260fs alleles completely impair the hydrolysis of clopidogrel and 2-oxo-clopidogrel (64). In addition, the *CES1* G143E variant recently has been associated with significantly higher active clopidogrel metabolite levels and enhanced inhibition of ADP-simulated platelet aggregation (39). Interestingly, the effect size of this uncommon allele on *ex vivo* platelet aggregation was approximately two-fold greater than *CYP2C19*2* (39). A trend toward lower cardiovascular event rates among G143E carriers was also observed; however, this was not statistically significant given the low allele frequency (39). Further studies are warranted to evaluate the effect of *CES1* variants on clinical outcomes during clopidogrel therapy.

P2RY12

Clopidogrel exerts its mechanism of action by specifically and irreversibly binding to the platelet $P2RY_{12}$ purinergic receptor (encoded by *P2RY12*), and inhibiting ADP-mediated platelet activation and aggregation. Two functional *P2RY12* haplotypes (H1 and H2) have been identified based on four variants in complete linkage disequilibrium (c.-15+137T>C, c.-15+742C>T, c.-15+799delA, c.36T>G) (43). The minor H2 haplotype was associated with increased platelet aggregation in response to ADP in healthy subjects (43). Recent studies have also suggested a link to peripheral arterial disease risk (65) and a possible association with increased *P2RY12* expression (66). However, some studies investigating the influence of these alleles in connection with clopidogrel response have concluded that the H2 haplotype has no influence on platelet function after treatment with a 600 mg (67) or 300 mg (68, 69) clopidogrel loading dose, or following a longer clopidogrel regime (70) among patients undergoing PCI. In contrast, a healthy volunteers study did identify a minor effect of the H2/H2 genotype based on a significant decrease in inhibition of platelet aggregation compared to H1/H1 and H1/H2 individuals following a week of clopidogrel exposure (75mg/day) (71). Similarly, clopidogrel-treated ACS/PCI patients homozygous for the H2 allele exhibited significantly higher platelet aggregation than patients with at least one H1 allele and were more frequently non-responders (72). Further studies have failed to show associations, including a link to clinical outcomes (5, 57, 73, 74). Based on the conflicting evidence, a clinically relevant influence of common *P2RY12* variants on clopidogrel efficacy is unlikely.

PON1

Paraoxonase 1 (PON1) encodes an esterase and is named after its ability to hydrolyze paroxon as part of the detoxification of the organophosphorus compound parathion. Two *PON1* polymorphisms, rs662 (c.575A>G; Q192R) and rs854560 (c.163T>A; L55M), are commonly studied as both previously have been associated with enzyme activity (75, 76). PON1 is largely expressed in the liver and is associated with high-density lipoprotein (HDL) particles in human plasma. *PON1* polymorphisms may modulate the effectiveness of HDL particles in protecting low density lipoprotein (LDL) against oxidative modification, which also may affect atherosclerosis risk (77). Notably, *PON1* was previously reported to be the rate-limiting enzyme in the sequential transformation of clopidogrel to its active thiol metabolite (45). In this study, 192Q homozygotes had a significantly higher risk of stent thrombosis compared to 192R homozygotes, lower PON1 plasma activity, lower plasma concentrations of the active metabolite

and lower platelet inhibition (45). Moreover, the unadjusted hazard ratio for risk of stent thrombosis among 192Q versus 192R homozygotes was 12.8 (95% CI, 4.74-90.91) in the discovery cohort and 10.2 (95% CI, 4.39-71.43) in the replication cohort (45).

However, multiple studies failed to replicate the reported association between *PON1* Q192R and active metabolite isomer H4 (clopi-H4) concentration (46), platelet function (46, 47, 56, 78), and cardiovascular outcomes or stent thrombosis during clopidogrel treatment (46-49, 58, 79, 80). Furthermore, a meta-analysis that included 17 studies did not support any association between *PON1* genotype and on-treatment platelet reactivity or cardiovascular events among clopidogrel-treated coronary patients (53). The reason for these conflicting results remains unclear but may be due to several factors including differences in study design (53, 79, 81). Additionally, available evidence suggests that *PON1* may actually be implicated in underlying cardiovascular disease risk (79), and/or in the formation of a thiol metabolite that has no involvement in antiplatelet response (52). Taken together, the vast majority of data does not support a role for *PON1* as an independent predictor of clopidogrel response and indicate that further study is warranted to determine its possible role in cardiovascular disease risk.

Linking Genetic Variability to Variability in Drug-Related Phenotypes

Clopidogrel response is a highly heritable trait (3) and *CYP2C19*2* has been associated with lower active metabolite exposure in clopidogrel treated subjects (2, 32, 82-84). Furthermore, *CYP2C19*2* and other loss-of-function variants have been associated with decreased platelet responsiveness to clopidogrel *ex vivo* (1-3, 5, 7, 28, 30, 73, 85). Importantly, a genome-wide association study identified *CYP2C19*2* as the major genetic determinant for clopidogrel response, which accounted for ~12% of the association with diminished platelet response (3). Further support for the role of *CYP2C19* in clopidogrel response variability comes from several meta-analyses, which concluded that ACS/PCI patients who carry *CYP2C19* loss-of-function alleles are at increased risk of major adverse cardiovascular events including stent thrombosis (6, 7, 86), even among heterozygotes (6, 7) (**Supplemental Table S7**).

Importantly, lack of effect of *CYP2C19* loss-of-function alleles on adverse cardiovascular outcomes has been reported among clopidogrel-treated patients with lower clinical risks; i.e., in studies with fewer patients undergoing PCI with stenting, and in patients receiving clopidogrel for atrial fibrillation and stroke (87, 88). Consistent with these findings, recent meta-analyses that include the clinical trials with low frequencies of PCI have not been able to support a major role for *CYP2C19* in clopidogrel response variability (89) (**Supplemental Table S7**). Consequently, widespread adoption of *CYP2C19*-guided antiplatelet therapy is not recommended. Rather, this guideline is an example of indication-specific clinical pharmacogenetics whereby *CYP2C19* genotype-directed antiplatelet therapy is limited predominantly to ACS patients undergoing PCI (90, 91). Although there is limited data regarding the potential role of *CYP2C19* for elective PCI cases treated with clopidogrel, these guidelines may also be considered for these patients; however, the lack of FDA-approved indication for prasugrel and ticagrelor for treatment of elective PCI must be balanced with the boxed warning on the clopidogrel label recommending consideration of alternative antiplatelet therapy in poor metabolizers with ACS *or* PCI.

Studies linking *CYP2C19* genotype with variability in clopidogrel response (phenotype) are summarized in **Supplemental Tables S6-S8**, and it is this body of evidence, rather than randomized clinical trials, which provides the basis for the therapeutic recommendations in **Table 2**. These supplemental tables were subdivided based on those studies reporting *CYP2C19* genotype and platelet function/clinical outcomes (**Table S6**), meta-analyses (**Table S7**) and clopidogrel dose escalation (**Table S8**). With alternatives to standard clopidogrel treatment available (e.g., prasugrel, ticagrelor), these studies offer a compelling rationale for pharmacogenetic-guided antiplatelet drug selection for ACS/PCI patients (13, 16).

CYP2C19 Genetic Test Interpretation and Suggested Clinical Actions

The American College of Cardiology Foundation/American Heart Association previously outlined possible actions by clinicians in response to the boxed warning (16). The article did not recommend *CYP2C19* genetic testing, citing the absence of prospective randomized clinical outcomes trials of genotype-directed antiplatelet therapy. Despite the lack of prospective randomized trials at the time of this writing, the substantial body of evidence from the current literature and potentially more efficacious antiplatelet therapy alternatives currently available may prompt some physicians to modify therapy based on genotype. Additionally, given the current availability of direct-to-consumer genetic testing and other sequencing programs, an increasing number of patients in the near future may already know their *CYP2C19* genotype status at the time of treatment.

It has been suggested that patients considered at moderate or high clinical risk for poor outcomes in the setting of sub-optimal antiplatelet therapy would benefit most from *CYP2C19* genotype-directed therapy. This includes, for example, patients undergoing high-risk multi-vessel PCI procedures, those who have already had an adverse outcome (e.g., stent thrombosis), and/or those with other high-risk clinical (e.g., ACS, diabetes mellitus, chronic kidney failure) or angiographic features.

Levels of Evidence Linking Genotype to Phenotype

Based on previously published criteria (92), a simple scale of high, moderate or weak, to grade the levels of evidence has been implemented:

- **High:** Evidence includes consistent results from well-designed, well-conducted studies.
- **Moderate:** Evidence is sufficient to determine effects, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies; generalizability to routine practice; or indirect nature of the evidence.
- **Weak:** Evidence is insufficient to assess the effects on health outcomes because of limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or lack of information.

Every effort was made to present evidence from high-quality studies and to take into consideration all available peer-reviewed published literature, which provided the framework for the strength of therapeutic recommendations.

Strength of Therapeutic Recommendations

CPIC's therapeutic recommendations are based on weighting the evidence from a combination of preclinical functional and clinical data, as well as on existing disease-specific consensus guidelines. Some of the factors that are taken into account in evaluating the evidence supporting therapeutic recommendations include: *in vivo* clinical outcome data for clopidogrel, *in vivo* pharmacokinetic and pharmacodynamic data for clopidogrel, *in vitro* enzyme activity of expressed wild-type or variant-containing CYP2C19, *in vitro* CYP2C19 enzyme activity from tissues isolated from individuals of known *CYP2C19* genotypes, *in vivo* pre-clinical pharmacokinetic and pharmacodynamic studies, and *in vitro* studies of CYP2C19 protein stability or enzyme activity.

Overall, the therapeutic recommendations are simplified to allow rapid interpretation by clinicians. CPIC uses a slight modification of a transparent and simple system for just three categories for recommendations adopted from the rating scale for evidence-based recommendations on the use of retroviral agents (**http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf**): 'strong', where "the evidence is high quality and the desirable effects clearly outweigh the undesirable effects"; 'moderate', in which "there is a close or uncertain balance" as to whether the evidence is high quality and the desirable clearly outweigh the undesirable effects; and 'optional', in which the desirable effects are closely balanced with undesirable effects and there is room for differences in opinion as to the need for the recommended course of action (93, 94).

- **'Strong' recommendation for the statement**
- **'Moderate' recommendation for the statement**
- **'Optional' recommendation for the statement**

Supplemental Table S1. Commonly tested *CYP2C19* variant alleles and their effect on CYP2C19 protein

Allele[1]	Major Nucleotide Variation	dbSNP Number[2]	Effect on CYP2C19 Protein
1	-	-	-
2	c.681G>A	rs4244285	Splicing defect
3	c.636G>A	rs4986893	W212X
4[3]	c.1A>G	rs28399504	M1V
5	c.1297C>T	rs56337013	R433W
6	c.395G>A	rs72552267	R132Q
7	c.819+2T>A	rs72558186	Splicing defect
8	c.358T>C	rs41291556	W120R
17[4]	c.-806C>T	rs12248560	Increased expression

[1] See Human Cytochrome P450 Allele Nomenclature Committee (http://www.cypalleles.ki.se) for comprehensive haplotype definitions of *CYP2C19* variant alleles and updated allele information.
[2] RefSNP accession ID number (http://www.ncbi.nlm.nih.gov/snp/).
[3] Of note, the *CYP2C19*4* loss-of-function allele has been identified in linkage disequilibrium with **17* (c.-806C>T) in certain ethnic subpopulations and this haplotype is designated *CYP2C19*4B* (38).
[4] There is linkage disequilibrium between c.681G and c.-806T (e.g., |D'|=1.0 and r^2=0.064 in CEU HapMap sample; |D'|=1.0 and r^2=0.065 in YRI HapMap sample; and |D'|=1.0 and r^2=0.074 in CHB HapMap sample). This means that the less common **17* variant (c.-806T) always tracks on the same allele with the more common c.681G. This complicates any interpretation of whether these two variants act independently of one another, and published articles argue both for (29, 35) and against (15, 36, 37) this point.

Supplemental Table S2. Association between *CYP2C19* allelic variants and enzyme activity

Functional Status	Alleles	References
Functional / normal activity / wild-type[1]	**1*	(95)
Loss-of-function / no or decreased activity	**2, *3, *4, *5, *6, *7, *8*	(96-102)
Increased function / increased activity	**17*	(103-105)

[1] An important caveat for all genotyping tests is that the "wild-type" (**1*) status is reported if all other alleles that are measured are absent. Some genotype tests do not interrogate the rare loss-of-function alleles and therefore, if present, would be erroneously reported as "wild-type". It is also possible that a novel un-interrogated *CYP2C19* sequence variant may confer altered enzyme function in an individual, and thus lead to the possibility of a loss-of-function allele being erroneously called as "wild-type" (**1*).

Supplemental Table S3. Frequencies[1] of *CYP2C19* alleles in major race/ethnic groups[2]

Allele	African	American	East Asian	European	Middle Eastern	Oceanian	South/Central Asian
1[3]	0.68	0.69	0.60	0.63	0.87	0.24	0.62
2	0.15	0.12	0.29	0.15	0.12	0.61	0.35
3	0.0052	0.00028	0.089	0.0042	0.011	0.15	0.024
4	0.00093	0.0024	0.00049	0.0025	ND	ND	0.00
5	ND	0.00	0.00062	0.000073	ND	ND	0.00
6	0.00	0.00	0.00	0.00017	ND	ND	0.00
7	ND	ND	ND	0.00	ND	ND	ND
8	0.00	0.0012	0.00	0.0035	ND	ND	ND
17	0.16	0.18	0.027	0.21	ND	ND	ND

ND: not determined.

[1] Average frequencies are based on actual numbers of subjects with each allele reported in multiple studies. See **Supplemental Table S4** for details and references.

[2] Worldwide race/ethnic designations correspond to the Human Genome Diversity Project-Centre Etude Polymorphism Humain (HGDP-CEPH) (21, 22) as indicated in **Supplemental Table S4**.

[3] Note that because *CYP2C19*1* is not genotyped directly, its inferred frequency is calculated as: 1 - (sum of variant allele frequencies).

Supplemental Table S4. *CYP2C19* minor allele frequencies

HGDP-CEPH Grouping[1]	Ethnicity	PMID[2]	CYP2C19 minor allele frequency (%)[3]								Total Individuals	Total Alleles	CYP2C19 minor alleles reported[3]							
			*2	*3	*4	*5	*6	*7	*8	*17[4]			*2	*3	*4	*5	*6	*7	*8	*17[4]
Africa	African	20173083	**19.2**	**0.2**	**0**	**-**	**0**	**-**	**0**	**-**	250	500	96	1	0	-	0	-	0	-
Africa	African American	16815315	**18.2**	**0.8**	**-**	**-**	**-**	**-**	**-**	**-**	236	472	86	4	-	-	-	-	-	-
Africa	African-American	9110363	**25**	**0**	-	-	-	-	-	-	108	216	54	0	-	-	-	-	-	-
Africa	African-American	19169185	**18.3**	**0.1**	-	-	-	-	-	-	441	882	161	1	**-**	**-**	**-**	**-**	**-**	-
Africa	African-American	8873222	19.1	-	-	-	-	-	-	-	76	152	**29**	-	-	-	-	-	-	-
Africa	African-American	8823231	16.0	-	-	-	-	-	-	-	100	200	**32**	-	-	-	-	-	-	-
Africa	Beninese	14616425	**13**	-	-	-	-	-	-	-	111	222	29	-	-	-	-	-	-	-
Africa	Black	21247447	19.9	0		-	0	-	0	-	289	578	**115**	**0**	**1**	**-**	**0**	**-**	**0**	**120**
Africa	Cape Mixed Ancestry	20712527	**17**	**7**	-	-	-	-	-	**14**	75	150	26	11	-	-	-	-	-	21
Africa	Egyptian	12047484	10.9	0.2	-	-	-	-	-	-	247	494	**54**	**1**	-	-	-	-	-	-
Africa	Ethiopian	9014201	**14**	**2**	-	-	-	-	-	-	114	228	32	5	-	-	-	-	-	-
Africa	Ethiopian	12142727	12.1	2.9	-	-	-	-	-	-	70	140	**17**	**4**	-	-	-	-	-	-
Africa	Ethiopian	16413245	-	-	-	-	-	-	-	13.2	190	380	**-**	**-**	-	-	-	-	-	**50**
Africa	Ghanaian	19954515	5.9	0	-	-	-	-	-	-	169	338	**20**	**0**	**-**	**-**	**-**	**-**	**-**	**-**
Africa	Nigerian	20831548	15.5	0	-	-	-	-	-	-	158	316	**49**	**0**	-	-	-	-	-	-
Africa	South African (Venda)	11372584	21.7	0	-	-	-	-	-	-	76	152	**33**	**0**	-	-	-	-	-	-
Africa	Tanzanian	10510152	**10**	**0**	-	-	-	-	-	-	195	390	39	0	-	-	-	-	-	-
Africa	Tanzanian	9797796	**17.9**	**0.6**	-	-	-	-	-	-	251	502	90	3	-	-	-	-	-	-
Africa	Tanzanian	11372584	18.0	0.3	-	-	-	-	-	-	192	384	**69**	**1**	-	-	-	-	-	-
Africa	Tunisian	18423013	10.5	-	-	-	-	-	-	-	544	1088	**114**	**-**	-	-	-	-	-	**-**
Africa	Ugandan	19002442	12.6	1.0	-	-	-	-	-	17.2	99	198	**25**	**2**	**-**	**-**	**-**	**-**	**-**	**34**
Africa	Xhosa	20712527	**21**	**0**	-	-	-	-	-	**10**	100	200	42	0	-	-	-	-	-	20
Africa	Zimbabwean Shona	7781265	4.2	-	-	-	-	-	-	-	84	168	**7**	-	-	-	-	-	-	-
Americas	Bolivian	15776277	7.8	0.1	-	-	-	-	-	-	778	1556	**121**	**1**	-	-	-	-	-	-
Americas	Brazilian (mixed)	21247447	16.1	0	**0.3**	0	-	-	-	19.2	1212	2424	**390**	**0**	7	**0**	-	-	-	**466**
Americas	Brazilian (mixed)	21173785	13.2	-	-	-	-	-	-	-	1034	2068	**273**	**1**	**-**	**-**	**-**	**-**	**-**	**358**
Americas	Columbian Mestizo	17623107	8.7	0	0	0	0	-	0	-	189	378	**33**	**0**	**0**	**0**	**0**	**-**	**0**	**-**
Americas	Mexican Americans	16815315	**9.7**	**0.1**	**-**	**-**	**-**	**-**	**-**	**-**	346	692	67		**-**	**-**	**-**	**-**	**-**	**-**
Americas	Native Canadian Indian	9797794	8.8	0	-	-	-	-	-	-	159	318	**28**	**0**	-	-	-	-	-	-
Americas	White Hispanic	21247447	12.6	0	0.2	-	0	-	0.2	14.0	242	484	**61**	**0**	**1**	**-**	**0**	**-**	**1**	**68**
East Asia	Bai Chinese	9103550	**25.7**	**5.2**	-	**0.3**	-	-	-	-	202	404	104	21	-	1	-	-	-	-

HGDP-CEPH Grouping[1]	Ethnicity	PMID[2]	CYP2C19 minor allele frequency (%)[3]								Total Individuals	Total Alleles	CYP2C19 minor alleles reported[3]							
			*2	*3	*4	*5	*6	*7	*8	*17[4]			*2	*3	*4	*5	*6	*7	*8	*17[4]
East Asia	Burmese	16946555	**30**	**4**	-	-	-	-	-	-	127	254	76	10	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Chinese	15327595	23.1	4.6	-	-	-	-	-	-	54	108	**25**	**5**	-	-	-	-	-	-
East Asia	Chinese	18231117	**29.7**	**3.5**	**0**	**0**	**-**	**-**	**-**	**0.5**	101	202	60	7	0	0	-	-	-	1
East Asia	Chinese	19636337	**25.5**	**2**	**0.5**	**-**	**-**	**-**	**-**	**3**	100	200	51	4	4	-	-	-	-	6
East Asia	Chinese	20173083	**30.7**	**4.5**	**0**	**-**	**0**	**-**	**0**	**-**	398	796	244	36	0	-	0	-	0	-
East Asia	Chinese	16855453	30.2	6.6	-	-	-	-	-	-	53	106	**32**	**7**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Chinese	17450472	29.7	5.9	-	-	-	-	-	-	59	118	**35**	**7**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Chinese	11686476	44.2	4.5	-	-	-	-	-	-	121	242	**107**	**11**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Chinese	19745563	24.8	7.0	-	-	-	-	-	-	107	214	**53**	**15**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Chinese	20831535	30.6	3.7	-	-	-	-	-	-	204	408	**125**	**15**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Chinese	19756559	30.7	7.1	-	-	-	-	-	-	287	574	**176**	**41**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Chinese	21163112	23.1	-	-	-	-	-	-	-	722	1444	**334**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Chinese	15301728	**35**	**7**	-	-	-	-	-	-	70	140	49	10	-	-	-	-	-	-
East Asia	Dai Chinese	11956668	**30.3**	**3.4**	-	-	-	-	-	-	386	772	234	26	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	East Asian	20173083	**32.4**	**8**	**0**	**-**	**0**	**-**	**0**	**-**	246	492	159	39	0	-	0	-	0	-
East Asia	East Asian	16815315	**28.9**	**9.6**	-	-	-	-	-	-	161	322	93	31	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Han Chinese	18518848	**24.7**	**3.3**	**-**	**-**	**-**	**-**	**-**	**1.6**	400	800	198	26	-	-	-	-	-	13
East Asia	Han Chinese	19444287	29.1	7.3	-	-	-	-	-	-	103	206	**60**	**15**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Han Chinese	15612662	34.1	8.2	-	-	-	-	-	-	104	208	**71**	**17**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Han Chinese	9103550	**36.6**	**7.4**	-	-	-	-	-	-	101	202	74	15	-	-	-	-	-	-
East Asia	Han Chinese	10585366	**30.7**	**3.8**	**0.4**	**0**	-	-	-	-	119	238	73	9	9	0	-	-	-	-
East Asia	Japanese	19881258	14.5	8.2	-	-	-	-	-	-	55	110	**16**	**9**	-	-	-	-	-	-
East Asia	Japanese	20173083	**30.3**	**13.1**	**0**	**-**	**0.1**	**-**	**0**	**-**	500	1000	303	131	0	-		-	0	-
East Asia	Japanese	16141610	26.7	12.8	-	-	-	-	-	-	253	506	**135**	**65**	**-**	**-**	**-**	**-**	**-**	**4**
East Asia	Japanese	9867757	28.2	6.5	-	-	-	-	-	-	62	124	**35**	**8**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Japanese	16595916	28.7	8.3	-	-	-	-	-	-	54	108	**31**	**9**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Japanese	20528170	32.4	10.8	-	-	-	-	-	-	51	102	**33**	**11**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Japanese	16338280	34.1	11.1	-	-	-	-	-	-	63	126	**43**	**14**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Japanese	10579481	25.5	6.5	-	-	-	-	-	-	108	216	**55**	**14**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Japanese	12386647	30.0	11.5	-	-	-	-	-	-	65	130	**39**	**15**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Japanese	11477314	29.4	11.3	-	-	-	-	-	-	80	160	**47**	**18**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Japanese	19259653	24.6	9.3	-	-	-	-	-	-	124	248	**61**	**23**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Japanese	17377957	20.5	17.1	-	-	-	-	-	-	73	146	**30**	**25**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Japanese	11434512	28.2	12.9	-	-	-	-	-	-	101	202	**57**	**26**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Japanese	11686476	26.0	14.6	-	-	-	-	-	-	96	192	**50**	**28**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Japanese	9860067	24.6	10.4	-	-	-	-	-	-	134	268	**66**	**28**	**-**	**-**	**-**	**-**	**-**	**-**

HGDP-CEPH Grouping[1]	Ethnicity	PMID[2]	CYP2C19 minor allele frequency (%)[3]								Total Individuals	Total Alleles	CYP2C19 minor alleles reported[3]							
			*2	*3	*4	*5	*6	*7	*8	*17[4]			*2	*3	*4	*5	*6	*7	*8	*17[4]
East Asia	Japanese	15952098	31.6	11.3	-	-	-	-	-	-	141	282	**89**	**32**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Japanese	15710002	24.0	11.0	-	-	-	-	-	-	173	346	**83**	**38**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Japanese	9511186	23.4	11.1	-	-	-	-	-	-	175	350	**82**	**39**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Japanese	21168310	30.8	10.0	-	-	-	-	-	-	201	402	**124**	**40**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Japanese	8988068	28.8	12.4	-	-	-	-	-	-	186	372	**107**	**46**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Japanese	14568772	27.3	12.0	-	-	-	-	-	-	196	392	**107**	**47**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Japanese	19156902	31.7	13.5	-	-	-	-	-	-	178	356	**113**	**48**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Japanese	16307177	29.6	12.8	-	-	-	-	-	-	203	406	**120**	**52**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Japanese	11240980	31.0	10.9	-	-	-	-	-	-	261	522	**162**	**57**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Japanese	17215846	27.8	12.3	-	-	-	-	-	-	300	600	**167**	**74**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Japanese	15017629	28.7	11.6	-	-	-	-	-	-	350	700	**201**	**81**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Japanese	17357148	27.7	14.3	-	-	-	-	-	-	352	704	**195**	**101**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Japanese	16268979	27.6	13.1	-	-	-	-	-	-	426	852	**235**	**112**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Japanese	17052843	31.1	14.6	-	-	-	-	-	-	487	974	**303**	**142**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Japanese	16338278	15.4	-	-	-	-	-	-	-	205	410	**63**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Japanese	21102498	**28.4**	-	-	-	-	-	-	-	58	116	33	**-**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Japanese	9110363	**23**	**10.4**	-	-	-	-	-	-	53	106	24	11	-	-	-	-	-	-
East Asia	Japanese	8807668	**27.4**	**10.8**	-	-	-	-	-	-	217	434	119	47	-	-	-	-	-	-
East Asia	Japanese	9631918	**35**	**11**	-	-	-	-	-	-	140	280	98	31	-	-	-	-	-	-
East Asia	Japanese	8890945	**21.9**	**11.7**	-	-	-	-	-	-	233	466	102	55	-	-	-	-	-	-
East Asia	Japanese	17502835	**31.1**	**12.6**	-	-	-	-	-	-	103	206	64	26	-	-	-	-	-	-
East Asia	Japanese	11763000	**27.5**	**12.8**	-	-	-	-	-	-	51	102	28	13	-	-	-	-	-	-
East Asia	Japanese	19696793	**26**	**13**	-	-	-	-	-	-	219	438	114	57	-	-	-	-	-	-
East Asia	Japanese	15691505	**32.7**	**13.7**	-	-	-	-	-	-	139	278	91	38	-	-	-	-	-	-
East Asia	Japanese	19696793	**31**	**18**	-	-	-	-	-	-	184	368	114	66	-	-	-	-	-	-
East Asia	Japanese	18241287	-	-	-	-	-	-	-	1.3	265	530	-	-	-	-	-	-	-	**7**
East Asia	Japanese (1st generation)	18231117	**26.2**	**10**	**0**	**0**	**-**	**-**	**-**	**1**	105	210	55	21	0	0	-	-	-	2
East Asia	Japanese (3rd generation)	18231117	**33.1**	**13.3**	**0**	**0**	**-**	**-**	**-**	**1.2**	84	168	56	22	0	0	-	-	-	2
East Asia	Japanese (native)	18231117	**34.5**	**9**	**0**	**0**	**-**	**-**	**-**	**0.5**	100	200	69	18	0	0	-	-	-	1
East Asia	Japanese (mixed descendents)	19882083	25.9	11.9	-	-	-	-	-	-	139	278	**72**	**33**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Karen	16946555	**28**	**1**	-	-	-	-	-	-	131	262	73	-	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Kazakh Chinese	19444287	15.4	7.9	-	-	-	-	-	-	107	214	**33**	**17**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Korean	18231117	**25**	**8**	**0**	**0**	**-**	**-**	**-**	**1.5**	100	200	50	16	0	0	-	-	-	3
East Asia	Korean	20499227	**16**	**-**	**-**	**-**	**-**	**-**	**-**	**20**	150	300	48	**-**	-	-	-	-	-	60
East Asia	Korean	20173083	**28.6**	**7.4**	**0**	**-**	**0**	**-**	**0**	**-**	200	400	114	30	0	-	0	-	0	-
East Asia	Korean	17424941	31.1	7.6	-	-	-	-	-	-	66	132	**41**	**10**	**-**	**-**	**-**	**-**	**-**	**-**

HGDP-CEPH Grouping[1]	Ethnicity	PMID[2]	CYP2C19 minor allele frequency (%)[3]								Total Individuals	Total Alleles	CYP2C19 minor alleles reported[3]							
			*2	*3	*4	*5	*6	*7	*8	*17[4]			*2	*3	*4	*5	*6	*7	*8	*17[4]
East Asia	Korean	19220726	34.9	6.6	-	-	-	-	-	-	136	272	**95**	**18**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Korean	17562299	21.1	9.8	-	-	-	-	-	-	97	194	**41**	**19**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Korean	20650435	31.0	8.7	-	-	-	-	-	-	126	252	**78**	**22**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Korean	20724801	31.3	6.5	-	-	-	-	-	-	176	352	**110**	**23**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Korean	9014204	20.9	11.7	-	-	-	-	-	-	103	206	**43**	**24**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Korean	14695703	26.7	10.3	-	-	-	-	-	-	116	232	**62**	**24**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Korean	20823393	34.0	9.7	-	-	-	-	-	-	134	268	**91**	**26**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Korean	21075428	30.3	6.8	-	-	-	-	-	-	190	380	**115**	**26**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Korean	19891553	-	8.8	-	-	-	-	-	-	226	452	**-**	**40**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Korean	18637061	26.0	8.7	-	-	-	-	-	-	327	654	**170**	**57**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Korean	17667801	28.2	7.6	-	-	-	-	-	-	377	754	**213**	**57**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Korean	19576320	27.3	9.3	-	-	-	-	-	-	387	774	**211**	**72**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Korean	20559522	29.9	9.5	-	-	-	-	-	-	463	926	**277**	**88**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Korean	21054462	28.4	10.1	-	-	-	-	-	1.5	271	542	**154**	**55**	**-**	**-**	**-**	**-**	**-**	**8**
East Asia	Li Chinese	17439410	35.8	3.0	-	-	-	-	-	-	165	330	**118**	**10**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Malay	15327595	30.9	10.3	-	-	-	-	-	-	68	136	**42**	**14**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Mongolian Chinese	20857895	24.3	4.3	-	-	-	-	-	-	280	560	**136**	**24**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Northeastern Thai	11927837	26.6	2.3	-	-	-	-	-	-	107	214	**57**	**5**	-	-	-	-	-	-
East Asia	Southeast Asian	16815315	**31.2**	**5.7**	-	-	-	-	-	-	80	160	50	9	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Taiwanese	20350136	**32**	**2.5**	-	-	-	-	-	**0.5**	100	200	64	5	-	-	-	-	-	1
East Asia	Taiwanese	16924387	32.2	5.0	-	-	-	-	-	-	180	360	**116**	**18**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Taiwanese	20457439	57.9	20.0	-	-	-	-	-	-	95	190	**110**	**38**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Taiwanese	15385837	**34**	**5.3**	-	-	-	-	-	-	169	338	115	18	-	-	-	-	-	-
East Asia	Taiwanese	9110363	**32**	**5.5**	-	-	-	-	-	-	118	236	76	13	-	-	-	-	-	-
East Asia	Thai	11686476	34.7	4.5	-	-	-	-	-	-	121	242	**84**	**11**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Thai	20358205	24.6	**-**	-	-	-	-	-	-	71	142	**35**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Thai	16946555	**29**	**3**	-	-	-	-	-	-	774	1548	449	46	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Vietnamese	18979093	30.6	6.3	-	-	-	-	-	-	72	144	**44**	**9**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Vietnamese	17667801	26.4	4.8	-	-	-	-	-	-	165	330	**87**	**16**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Vietnamese	11686476	26.7	13.3	-	-	-	-	-	-	90	180	**48**	**24**	**-**	**-**	**-**	**-**	**-**	**-**
Europe	Ashkenazi Jewish	18240905	15.2	**-**	1.8	**-**	**-**	**-**	**-**	**-**	250	500	**76**	**-**	**9**	**-**	**-**	**-**	**-**	**-**
Europe	Belgian	14616425	**9.1**	-	-	-	-	-	-	-	121	242	22	-	-	-	-	-	-	-
Europe	Bosnian	21108610	16.9	-	-	-	-	-	-	-	77	154	**26**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
Europe	Bulgarian	18021343	13.5	**-**	**-**	**-**	**-**	**-**	**-**	**-**	96	192	**26**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
Europe	Caucasian	18231117	**13.6**	**0**	**0.3**	**0**	**-**	**-**	**-**	**20.1**	143	286	39	0	1	0	**-**	**-**	**-**	57

HGDP-CEPH Grouping[1]	Ethnicity	PMID[2]	CYP2C19 minor allele frequency (%)[3]								Total Individuals	Total Alleles	CYP2C19 minor alleles reported[3]							
			*2	*3	*4	*5	*6	*7	*8	*17[4]			*2	*3	*4	*5	*6	*7	*8	*17[4]
Europe	Caucasian	19463375	13.3	-	2.5	-	-	-	-	20.8	60	120	**16**	**-**	**3**	**-**	**-**	**-**	**-**	**25**
Europe	Caucasian	18521743	**-**	**-**	**-**	**-**	**-**	**-**	**-**	23.1	1989	3978	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**919**
Europe	Caucasian	20173083	**15**	**0.1**	**0.1**	**-**	**0.1**	**-**	**0.1**	**-**	454	908	136	1	1	-		-	0	-
Europe	Caucasian	12823155	14.2	0	0	-	-	-	-	-	60	120	**17**	**0**	**0**	-	-	-	-	-
Europe	Caucasian	15590749	16.9	0	0	-	-	-	-	-	59	118	**20**	**0**	**0**	-	-	-	-	-
Europe	Caucasian	20857895	14.0	0	-	-	-	-	-	-	203	406	**57**	**0**	**-**	**-**	**-**	**-**	**-**	**-**
Europe	Caucasian	21047200	17.9	0	-	-	-	-	-	-	215	430	**77**	**0**	**-**	**-**	**-**	**-**	**-**	**-**
Europe	Caucasian	21108329	15.4	0.1	-	-	-	-	-	-	344	688	**106**	**1**	**-**	**-**	**-**	**-**	**-**	**-**
Europe	Caucasian	20064729	15.7	0.5	-	-	-	-	-	-	289	578	**91**	**3**	-	-	-	-	-	-
Europe	Caucasian	19337788	14.5	6.5	-	-	-	-	-	-	186	372	**54**	**24**	-	-	-	-	-	-
Europe	Caucasian	18496131	16.5	**-**	**-**	**-**	**-**	**-**	**-**	**-**	124	248	**41**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
Europe	Caucasian	20179710	15.2	-	-	-	-	-	-	-	230	460	**70**	-	-	-	-	-	-	-
Europe	Caucasian	18482659	16.4	**-**	**-**	**-**	**-**	**-**	**-**	**-**	797	1594	**262**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
Europe	Caucasian	11037802	14.0	-	-	-	-	-	-	-	952	1904	**267**	-	-	-	-	-	-	-
Europe	Caucasian	18521743	14.5	**-**	**-**	**-**	**-**	**-**	**-**	**-**	1960	3920	**570**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
Europe	Caucasian	16815315	**12.7**	**0.9**	**-**	**-**	**-**	**-**	**-**	**-**	273	546	69	5	-	-	-	-	-	**-**
Europe	Caucasian	19169185	**14.2**	**0**	**-**	**-**	**-**	**-**	**-**	**-**	3774	7548	1072	0	-	-	-	-	-	-
Europe	Central European	19581389	8.5	-	-	-	-	-	-	33.8	71	142	**12**	**-**	**-**	**-**	**-**	**-**	**-**	**48**
Europe	Croatian	12950145	15.0	-	-	-	-	-	-	-	200	400	**60**	-	-	-	-	-	-	-
Europe	Danish	20665013	15.0	-	-	-	-	-	-	20.1	276	552	**83**	**-**	**-**	**-**	**-**	**-**	**-**	**111**
Europe	Danish	16044105	13.8	0	**-**	**-**	**-**	**-**	**-**	**-**	69	138	**19**	**0**	-	-	-	-	-	-
Europe	Danish	19192051	13.0	0	-	-	-	-	-	-	300	600	**78**	**0**	-	-	-	-	-	-
Europe	Danish	9754988	16.5	0.0	-	-	-	-	-	-	303	606	**100**	**0**	-	-	-	-	-	-
Europe	Danish	20684753	**10.9**	-	-	-	-	-	-	-	339	678	74	-	-	-	-	-	-	-
Europe	Dutch	20531370	13.3	-	-	-	-	-	-	22.1	678	1356	**181**	**-**	**-**	**-**	**-**	**-**	**-**	**299**
Europe	Dutch	19884907	15.4	-	-	-	-	-	-	24.4	178	356	**55**	**-**	**-**	**-**	**-**	**-**	**-**	**87**
Europe	Dutch	19934793	16.8	0.2	-	-	-	-	-	-	428	856	**144**	**2**	-	-	-	-	-	-
Europe	Dutch	11829201	12.9	0.2	-	-	-	-	-	-	765	1530	**198**	**3**	-	-	-	-	-	-
Europe	Dutch	18854779	17.7	-	-	-	-	-	-	-	113	226	**40**	-	-	-	-	-	-	-
Europe	Dutch	17667959	**15**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	181	362	54	**-**	**-**	**-**	**-**	**-**	**-**	**-**
Europe	English	12419832	13.4	-	-	-	-	-	-	-	1082	2164	**291**	-	-	-	-	-	-	-
Europe	European	9435198	**13**	**0.3**	**0.6**	-	-	-	-	-	173	346	45	1	2	-	-	-	-	-
Europe	European-American	9110363	**13**	**0**	-	-	-	-	-	-	105	210	27	0	-	-	-	-	-	-
Europe	Faroese	20665013	18.6	-	-	-	-	-	-	15.4	311	622	**116**	**-**	**-**	**-**	**-**	**-**	**-**	**96**
Europe	Faroese	16025294	**18.8**	**0**	**-**	**-**	**-**	**-**	**-**	**-**	312	624	117	0	-	-	-	-	-	-
Europe	Finnish	16024198	**16.4**	**0**	**-**	**-**	**-**	**-**	**-**	**-**	177	354	58	0	-	-	-	-	-	-

HGDP-CEPH Grouping[1]	Ethnicity	PMID[2]	CYP2C19 minor allele frequency (%)[3]								Total Individuals	Total Alleles	CYP2C19 minor alleles reported[3]							
			*2	*3	*4	*5	*6	*7	*8	*17[4]			*2	*3	*4	*5	*6	*7	*8	*17[4]
Europe	Finnish	17635176	17.6	-	-	-	-	-	-	-	449	898	**158**	-	-	-	-	-	-	-
Europe	French	19496924	-	-	0.7	0	0.1	-	-	20.0	598	1196	-	-	**8**	**0**	**1**	-	-	**239**
Europe	French	18205890	18.4	-	-	-	-	-	-	-	359	718	**132**	-	-	-	-	-	-	-
Europe	French	20708365	17.6	-	-	-	-	-	-	-	411	822	**145**	-	-	-	-	-	-	-
Europe	French	18394438	15.7	-	-	-	-	-	-	-	603	1206	**189**	-	-	-	-	-	-	-
Europe	German	20492469	13.5	-	-	-	-	-	-	21.3	986	1972	**267**	-	-	-	-	-	-	**421**
Europe	German	20083681	-	-	-	-	-	-	-	22.9	1524	3048	-	-	-	-	-	-	-	**698**
Europe	German	18781853	15.1	0.0	-	-	-	-	-	25.7	423	846	**128**	**0**	-	-	-	-	-	**217**
Europe	German	20826260	14.4	-	-	-	-	-	-	-	928	1856	**268**	-	-	-	-	-	-	**417**
Europe	German	16116487	15.8	0	-	-	-	-	-	-	60	120	**19**	**0**	-	-	-	-	-	-
Europe	German	7663532	12.1	0	-	-	-	-	-	-	174	348	**42**	**0**	-	-	-	-	-	-
Europe	German	17680025	11.9	3.8	-	-	-	-	-	-	572	1144	**136**	**44**	-	-	-	-	-	-
Europe	German	14586385	15.6	-	-	-	-	-	-	-	96	192	**30**	-	-	-	-	-	-	-
Europe	German	15371981	18.3	-	-	-	-	-	-	-	131	262	**48**	-	-	-	-	-	-	-
Europe	German	19415824	15.0	-	-	-	-	-	-	-	533	1066	**160**	-	-	-	-	-	-	-
Europe	German	12713578	15.0	-	-	-	-	-	-	-	562	1124	**169**	-	-	-	-	-	-	-
Europe	German	20510210	16.3	-	-	-	-	-	-	-	760	1520	**248**	-	-	-	-	-	-	-
Europe	German	19193675	14.6	-	-	-	-	-	-	-	2485	4970	**727**	-	-	-	-	-	-	-
Europe	German	19424794	14.6	-	-	-	-	-	-	-	8609	17218	**2510**	-	-	-	-	-	-	-
Europe	German	16413243	**12.7**	-	**1**	-	-	-	-	-	51	102	13	-	1	-	-	-	-	-
Europe	Greek	19102714	13.1	0	-	-	-	-	-	19.6	283	566	**74**	**0**	-	-	-	-	-	**111**
Europe	Italian	20309015	14.3	-	-	-	-	-	-	17.6	182	364	**52**	-	-	-	-	-	-	**64**
Europe	Italian	15177309	**11.1**	**0**	-	-	-	-	-	-	360	720	80	0	-	-	-	-	-	-
Europe	Italian	12496751	12.4	-	-	-	-	-	-	-	93	186	**23**	-	-	-	-	-	-	-
Europe	Italian	19268736	17.7	-	-	-	-	-	-	-	772	1544	**273**	-	-	-	-	-	-	-
Europe	Italian	18004210	17.1	-	-	-	-	-	-	-	1419	2838	**485**	-	-	-	-	-	-	-
Europe	Norwegian	20565970	17.8	-	-	-	-	-	-	21.7	90	180	**32**	-	-	-	-	-	-	**39**
Europe	Norwegian	20665013	15.2	-	-	-	-	-	-	22.0	309	618	**94**	-	-	-	-	-	-	**136**
Europe	Norwegian	18677622	-	-	-	-	-	-	-	23.6	121	242	-	-	-	-	-	-	-	**57**
Europe	Norwegian	17625515	18.1	0.6	-	-	-	-	-	-	166	332	**60**	**2**	-	-	-	-	-	**73**
Europe	Norwegian	12835613	15.2	0	0	-	-	-	-	-	128	256	**39**	**0**	**0**	-	-	-	-	-
Europe	Norwegian	16418702	19.9	-	-	-	-	-	-	-	83	166	**33**	-	-	-	-	-	-	-
Europe	Polish	16912869	11.6	-	-	-	-	-	-	27.2	125	250	**29**	-	-	-	-	-	-	**68**
Europe	Polish	20376628	12.6	-	-	-	-	-	-	28.1	139	278	**35**	-	-	-	-	-	-	**78**
Europe	Polish	15976989	10.0	-	-	-	-	-	-	-	70	140	**14**	-	-	-	-	-	-	-
Europe	Polish	18577829	10.5	-	-	-	-	-	-	-	105	210	**22**	-	-	-	-	-	-	-

HGDP-CEPH Grouping[1]	Ethnicity	PMID[2]	CYP2C19 minor allele frequency (%)[3]								Total Individuals	Total Alleles	CYP2C19 minor alleles reported[3]							
			*2	*3	*4	*5	*6	*7	*8	*17[4]			*2	*3	*4	*5	*6	*7	*8	*17[4]
Europe	Polish	20924183	11.9	-	-	-	-	-	-	-	261	522	**62**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
Europe	Portuguese	9295062	13.1	0	-	-	-	-	-	-	153	306	**40**	**0**	-	-	-	-	-	-
Europe	Portuguese	18240903	**14**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	126	252	35	**-**	**-**	**-**	**-**	**-**	**-**	**-**
Europe	Russian	12879168	11.4	0.3	-	-	-	-	-	-	290	580	**66**	**2**	-	-	-	-	-	-
Europe	Russian	18061941	9.4	**-**	**-**	**-**	**-**	**-**	**-**	**-**	159	318	**30**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
Europe	Russian	20373852	13.1	-	-	-	-	-	-	-	352	704	**92**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
Europe	Siberian	18597650	**-**	3.5	**-**	**-**	**-**	**-**	**-**	**-**	437	874	**-**	**31**	**-**	**-**	**-**	**-**	**-**	**-**
Europe	Siberian	18597650	17.3	**-**	**-**	**-**	**-**	**-**	**-**	**-**	433	866	**150**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
Europe	Slovenian	18496682	10.5	**-**	**-**	**-**	**-**	**-**	**-**	32.9	105	210	**22**	**-**	**-**	**-**	**-**	**-**	**-**	**69**
Europe	Spanish	15728438	13.7	-	-	-	-	-	-	-	300	600	**82**	-	-	-	-	-	-	-
Europe	Spanish	16006997	13.9	-	-	-	-	-	-	-	672	1344	**187**	-	-	-	-	-	-	-
Europe	Swedish	20499227	**28**	**11**	**-**	**-**	**-**	**-**	**-**	**0.3**	185	370	104	41	-	-	-	-	-	1
Europe	Swedish	16413245	-	-	-	-	-	-	-	6.4	314	628	**-**	-	-	-	-	-	-	**40**
Europe	Swedish	19907421	14.5	-	0.1	-	-	-	-	17.7	713	1426	**207**	**-**	**1**	**-**	**-**	**-**	**-**	**252**
Europe	Swedish	20468063	15.1	-	-	-	-	-	-	19.0	1416	2832	**427**	**-**	**-**	**-**	**-**	**-**	**-**	**537**
Europe	Swedish	8747407	11.7	0.3	-	-	-	-	-	-	175	350	**41**	**1**	-	-	-	-	-	-
Europe	Swedish	9776439	14.5	0.4	-	-	-	-	-	-	245	490	**71**	**2**	-	-	-	-	-	-
Europe	Swedish	9772024	15.5	0	-	-	-	-	-	-	110	220	**34**	**4**	-	-	-	-	-	-
Europe	Swedish	9829356	12.6	1.4	-	-	-	-	-	-	143	286	**36**	**4**	-	-	-	-	-	-
Europe	Swiss	16338275	16.3	0.2	**-**	**-**	**-**	**-**	**-**	**-**	208	416	**68**	**1**	-	-	-	-	-	-
Europe	Swiss	17697139	13.8	**-**	**-**	**-**	**-**	**-**	**-**	**-**	94	188	**26**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
Europe	Swiss	17681590	17.9	**-**	**-**	**-**	**-**	**-**	**-**	**-**	81	162	**29**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
Europe	Swiss	11809184	13.4	-	-	-	-	-	-	-	123	246	**33**	-	-	-	-	-	-	-
Europe	Swiss	17178267	**16.7**	**0.1**	**-**	**-**	**-**	**-**	**-**	**-**	245	490	82	0	-	-	-	-	-	-
Europe	Turkish	10460072	**12**	**0.4**	**0**	**0**	-	-	-	-	404	808	97	3	0	0	-	-	-	-
Europe	Turkish	19499406	12.0	0	-	-	-	-	-	-	100	200	**24**	**0**	-	-	-	-	-	-
Europe	Turkish	17269966	11.5	0	**-**	**-**	**-**	**-**	**-**	**-**	169	338	**39**	**0**	**-**	**-**	**-**	**-**	**-**	**-**
Europe	Turkish	17290075	21.7	0	**-**	**-**	**-**	**-**	**-**	**-**	182	364	**79**	**0**	**-**	**-**	**-**	**-**	**-**	**-**
Europe	Turkish	20533108	11.4	5.2	-	-	-	-	-	-	105	210	**24**	**11**	**-**	**-**	**-**	**-**	**-**	**-**
Europe	Turkish	17868191	12.1	4.0	**-**	**-**	**-**	**-**	**-**	**-**	199	398	**48**	**16**	**-**	**-**	**-**	**-**	**-**	**-**
Europe	Turkish	11908757	9.4	8.9	-	-	-	-	-	-	96	192	**18**	**17**	-	-	-	-	-	-
Europe	Turkish	19821196	**13**	**1**	**-**	**-**	**-**	**-**	**-**	**-**	100	200	26	2	-	-	-	-	-	-
Europe	White	19106084	-	-	-	-	-	-	-	19.5	2164	4328	-	-	-	-	-	-	-	**844**
Europe	White	20801498	14.1	0.1	0.1	0.0	0.0	0	0.4	22.3	10285	20570	**2899**	**16**	**26**	**1**	**2**	**0**	**74**	**4590**
Europe	White	19106083	-	-	-	0.0	-	-	-	-	2176	4352	-	-	-	**1**	-	-	-	-
Europe	White	19106083	-	-	0.5	-	-	-	-	-	2189	4378	-	-	**21**	-	-	-	-	-

HGDP-CEPH Grouping[1]	Ethnicity	PMID[2]	CYP2C19 minor allele frequency (%)[3]								Total Individuals	Total Alleles	CYP2C19 minor alleles reported[3]							
			*2	*3	*4	*5	*6	*7	*8	*17[4]			*2	*3	*4	*5	*6	*7	*8	*17[4]
Europe	White	19106083	-	0.0	-	-	-	-	-	-	2187	4374	**-**	**1**	-	-	-	-	-	-
Europe	White	19106083	15.4	**-**	**-**	**-**	**-**	**-**	**-**	**-**	2178	4356	**670**	-	-	-	-	-	-	-
Europe	White/Non-Hispanic	21192344	13.3	0	0.4	-	0.0	-	0.4	22.5	1253	2506	**333**	**0**	**10**	**-**	**1**	**-**	**10**	**564**
Middle East	Bedouin	15651900	**12.0**	**1.0**	-	-	-	-	-	-	50	100	12	1	-	-	-	-	-	-
Middle East	Iranian	17201743	14.0	0.0	-	-	-	-	-	-	200	400	**56**	**0**	-	-	-	-	-	-
Middle East	Iranian	20804307	13.4	1.8	-	-	-	-	-	-	82	164	**22**	**3**	-	-	-	-	-	-
Middle East	Iranian	20637959	11.1	1.0	-	-	-	-	-	-	99	198	**22**	**2**	-	-	-	-	-	-
Middle East	Iranian	20885015	12.3	0.7	-	-	-	-	-	-	150	300	**37**	**2**	-	-	-	-	-	-
Middle East	Jewish Israeli	10096259	15.4	0.7	-	-	-	-	-	-	140	280	**43**	**2**	-	-	-	-	-	-
Middle East	Palestinian	19193970	7.1	2.6	-	-	-	-	-	-	252	504	**36**	**13**	-	-	-	-	-	-
Middle East	Saudi Arabians	9110363	**15.0**	**0.0**	-	-	-	-	-	-	97	194	29	0	-	-	-	-	-	-
Oceania	Filipinos	9110363	**39**	**7.7**	-	-	-	-	-	-	52	104	41	8	-	-	-	-	-	-
Oceania	Maori	18425152	**24**	**1.7**	**-**	**-**	**-**	**-**	**-**	**-**	60	120	29	2	**-**	**-**	**-**	**-**	**-**	**-**
Oceania	Sepik (pooled study)	14583683	**45**	**16**	-	-	-	-	-	-	401	802	361	127	-	-	-	-	-	-
Oceania	Vanuatuan (pooled study)	10591538	**63**	**15**	-	-	-	-	-	-	5638	11276	7132	1660	-	-	-	-	-	-
Oceania	Vanuatuan (pooled study)	9093256	70.8	13.3	-	-	-	-	-	-	493	986	**698**	**131**	-	-	-	-	-	-
Oceania	Western Australian Aboriginese	11207032	**35.5**	**14.3**	-	-	-	-	-	-	227	454	161	65	-	-	-	-	-	-
South/Central Asia	Maharashtrian (India)	17978853	46.0	1.1	-	-	-	-	-	-	139	278	**128**	**3**	-	-	-	-	-	-
South/Central Asia	North Indian	11014415	29.8	0	-	-	-	-	-	-	121	242	**72**	**0**	-	-	-	-	-	-
South/Central Asia	North Indian	20602612	36.3	0.4	-	-	-	-	-	-	457	914	**332**	**4**	**-**	**-**	**-**	**-**	**-**	**-**
South/Central Asia	North Indian	18644391	34.1	5.8	-	-	-	-	-	-	600	1200	**409**	**70**	-	-	-	-	-	-
South/Central Asia	North Indian	19954746	34.9	-	-	-	-	-	-	-	750	1500	**523**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
South/Central Asia	North Indian	19942749	29.1	-	-	-	-	-	-	-	91	182	**53**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
South/Central Asia	Pakistani	20102361	27.2	**-**	-	-	-	-	-	-	68	136	**37**	-	-	-	-	-	-	-
South/Central Asia	South Indian	15662508	36.7	0.5	0	0	0	-	-	-	300	600	**220**	**3**	**0**	**0**	**0**	-	-	-
South/Central Asia	South Indian	15660966	34.2	0.6	-	-	-	-	-	-	341	682	**233**	**4**	-	-	-	-	-	-
South/Central Asia	South Indian	20045989	**38**	**2**	**-**	**-**	**-**	**-**	**-**	**-**	50	100	38	2	-	-	-	-	-	-
South/Central Asia	South Indian	19430176	**37.1**	**2.5**	-	-	-	-	-	-	58	116	43	3	-	-	-	-	-	-
South/Central Asia	Tamilian	20390258	42.0	0.7	-	-	-	-	-	-	292	584	**245**	**4**	-	-	-	-	-	-
South/Central Asia	Tamilian	12919183	**37.9**	**2.2**	-	-	-	-	-	-	112	224	85	5	-	-	-	-	-	-
South/Central Asia	Uighur Chinese	20460345	-	2.4	-	-	-	-	-	-	706	1412	**-**	**34**	-	-	-	-	-	-
South/Central Asia	Uigur Chinese	15612662	49.0	1.6	-	-	-	-	-	-	96	192	**94**	**3**	-	-	-	-	-	-

HGDP-CEPH Grouping[1]	Ethnicity	PMID[2]	CYP2C19 minor allele frequency (%)[3]								Total Individuals	Total Alleles	CYP2C19 minor alleles reported[3]							
			*2	*3	*4	*5	*6	*7	*8	*17[4]			*2	*3	*4	*5	*6	*7	*8	*17[4]
South/Central Asia	Uygur Chinese	19444287	16.1	9.4	-	-	-	-	-	-	149	298	**48**	**28**	**-**	**-**	**-**	**-**	**-**	**-**

[1] Worldwide subpopulations and ethnicities were grouped based on the Human Genome Diversity Project-Centre Etude Polymorphism Humain (HGDP-CEPH) (21, 22).
[2] PMID is a unique PubMed Identifier number assigned to each PubMed citation of life sciences and biomedical scientific journal articles: http://www.ncbi.nlm.nih.gov/pubmed/.
[3] Data in bold were manually retrieved from each study; non-bold data were calculated and derived from the applicable reported (bold) data. Alleles not interrogated in a given study are noted by a dashed line ('-').
[4] Because the *CYP2C19*17* allele was identified in 2006 (103), *CYP2C19* studies prior to this date did not include this allele.

Supplemental Table S5. Predicted metabolizer phenotypes based on *CYP2C19* genotype and predicted average frequencies

	Predicted Metabolizer Phenotype (Average Multi-Ethnic Frequency[1])								
Allele	***1***	***2***	***3***	***4***	***5***	***6***	***7***	***8***	***17***
1	EM (35-50%)	IM (17-35%)	IM (1-11%)	IM (<1%)	IM (<1%)	IM (<1%)	IM (<1%)	IM (<1%)	UM (3-27%)
2		PM (2-8%)	PM (0-5%)	PM (<1%)	PM (<1%)	PM (<1%)	PM (<1%)	PM (<1%)	IM[2] (1-6%)
3			PM (<1%)	PM (<1%)	PM (<1%)	PM (<1%)	PM (<1%)	PM (<1%)	IM[2] (<1%)
4				PM (<1%)	PM (<1%)	PM (<1%)	PM (<1%)	PM (<1%)	IM[2] (<1%)
5					PM (<1%)	PM (<1%)	PM (<1%)	PM (<1%)	IM[2] (<1%)
6						PM (<1%)	PM (<1%)	PM (<1%)	IM[2] (<1%)
7							PM (<1%)	PM (<1%)	IM[2] (<1%)
8								PM (<1%)	IM[2] (<1%)
17									UM (1-5%)

EM: extensive metabolizer; IM: intermediate metabolizer; PM: poor metabolizer; UM: ultrarapid metabolizer.

[1] Frequencies of predicted metabolizer phenotypes were determined using the allele frequencies from **Supplemental Tables S3** and **S4** and the Hardy-Weinberg equation.

[2] The predicted metabolizer phenotype for these genotypes are provisional classifications. The currently available evidence indicates that the **17* gain-of-function allele is unable to completely compensate for the **2* loss-of-function allele (106); however, this data has not been consistently replicated and is therefore a provisional classification

Supplemental Table S6. Evidence linking *CYP2C19* genotype with clopidogrel response.

Type of Experimental Model	Major Findings	References	Level of Evidence*
In vitro	*CYP2C19*2* (c.681G>A; rs4244285) is a common polymorphism that results in a splicing defect and non-functional CYP2C19 protein.	de Morais, *et al*. 1994 (96)	High
In vitro	The *CYP2C19*3* - **8* variant alleles result in loss-of-function.	de Morais, *et al*. 1994 (97), Xiao, *et al*. 1997 (98), Ferguson, *et al*. 1998 (99), Ibeanu, *et al*. 1998 (100), Ibeanu, *et al*. 1998 (101), Ibeanu, *et al*. 1999 (102)	High
In vitro/In vivo	*CYP2C19*17* (c.-806C>T; rs12248560) is a common polymorphism that results in increased activity as a consequence of enhanced transcription.	Sim, *et al*. 2006 (103), Rudberg, *et al*. 2008 (104), Li-Wan-Po, *et al*. 2010 (105)	High
In vitro	CYP1A2, CYP2B6, CYP2C9, CYP2C19 and CYP3A4/5 are involved in the hepatic metabolism of clopidogrel.	Savi, *et al*. 1992 (107), Savi, *et al*. 2000 (108), Clarke, *et al.* 2003 (109), Farid, *et al*. 2007 (110), Kazui, *et al*. 2010 (111), Abell and Liu, 2011 (112)	High
In vitro	CYP2C19 contributes substantially to both oxidative steps of clopidogrel metabolism during the formation of its active metabolite.	Kazui, *et al*. 2010 (111)	High
Clinical	*CYP2C19*2* is associated with reduced formation of active metabolites (pharmacokinetics) in healthy subjects treated with clopidogrel.	Brandt, *et al.* 2007 (32), Kim, *et al*. 2008 (82), Umemura, *et al*. 2008 (83), Mega, *et al.* 2009 (2), Simon, *et al.* 2011 (57), Gong, *et al.* 2012 (52),	High

		Kelly, *et al.* 2012 (113)	
Clinical	*CYP2C19*2* is associated with reduced formation of active metabolites (pharmacokinetics) in ACS/PCI patients treated with clopidogrel.	Varenhorst, *et al*. 2009 (84), Collet, *et al.* 2011 (114)	High
Clinical	*CYP2C19*2* is associated with higher on-treatment platelet reactivity (pharmacodynamics) in healthy subjects treated with clopidogrel.	Hulot, *et al.* 2006 (1), Brandt, *et al.* 2007 (32), Fontana, *et al*. 2007 (115), Chen, *et al*. 2008 (116), Kim, *et al*. 2008 (82), Umemura, *et al*. 2008 (83), Mega, *et al.* 2009 (2), Shuldiner, *et al.* 2009 (3), Simon, *et al.* 2011 (57)	High
Clinical	*CYP2C19*2* is associated with higher on-treatment platelet reactivity (pharmacodynamics) in ACS/PCI patients treated with clopidogrel.	Giusti, *et al.* 2007 (73), Frere, *et al.* 2008 (33), Geisler, *et al.* 2008 (31), Trenk, *et al.* 2008 (30), Jinnai, *et al*. 2009 (117), Shuldiner, *et al.* 2009 (3), Varenhorst, *et al*. 2009 (84), Harmsze, *et al*. 2010 (41), Hochholzer, *et al*. 2010 (118), Jeong, *et al*. 2010 (119), Kang, *et al*. 2010 (120), Sibbing, *et al*. 2010 (106), Bouman, *et al.* 2011 (121), Collet, *et al.* 2011 (114), Cuisset, *et al.* 2011 (122), Gurbel, *et al.* 2011 (36), Hwang, *et al*. 2011 (123), Jeong, *et al*. 2011 (124), Maeda, *et al*. 2011 (125), Ono, *et al.* 2011 (126),	High

		Park, *et al.* 2011 (127), Rideg, *et al.* 2011 (128), Yamamoto, *et al.* 2011 (129), Bonello, *et al.* 2012 (130), Harmsze, *et al.* 2012 (131), Kassimis, *et al.* 2012 (132), Kim, *et al.* 2012 (133), Kreutz, *et al.* 2012 (78), Oh, *et al.* 2012 (134), Price, *et al.* 2012 (56), Tang, *et al.* 2012 (135), Wu, *et al.* 2012 (136), Zou, *et al.* 2012 (137)	
Clinical	*CYP2C19*2* is associated with adverse cardiovascular outcomes (e.g., cardiovascular death, myocardial infarction, stroke, stent thrombosis) in ACS/PCI patients treated with clopidogrel.	Trenk, *et al.* 2008 (30), Collet, *et al.* 2009 (28), Giusti, *et al*. 2009 (138), Mega, *et al.* 2009 (2), Shuldiner, *et al.* 2009 (3), Sibbing, *et al.* 2009 (4), Simon, *et al.* 2009 (5), Harmsze, *et al*. 2010 (139), Malek, *et al*. 2010 (140), Cayla, *et al.* 2011 (10), Jeong, *et al*. 2011 (124), Marcucci, *et al.* 2011 (141), Rideg, *et al.* 2011 (128), Yamamoto, *et al.* 2011 (129), Delaney, *et al.* 2012 (80), Oh, *et al.* 2012 (134), Teixeira, *et al.* 2012 (142), Wu, *et al.* 2012 (136), Zou, *et al.* 2012 (137)	High
Clinical	*CYP2C19*3* (and possibly other loss-of-function alleles) is	Kim, *et al*. 2008 (82),	High

	associated with lower formation of active metabolites (pharmacokinetics) in healthy subjects treated with clopidogrel.	Umemura, *et al*. 2008 (83), Mega, *et al.* 2009 (2), Kelly, *et al.* 2012 (113)	
Clinical	*CYP2C19*3* (and possibly other loss-of-function alleles) is associated with higher on-treatment platelet reactivity (pharmacodynamics) in healthy subjects treated with clopidogrel.	Chen, *et al*. 2008 (116), Kim, *et al*. 2008 (82), Umemura, *et al*. 2008 (83), Mega, *et al.* 2009 (2)	High
Clinical	*CYP2C19*3* (and possibly other loss-of-function alleles) is associated with higher on-treatment platelet reactivity (pharmacodynamics) in ACS/PCI patients treated with clopidogrel.	Jinnai, *et al*. 2009 (117), Lee, *et al*. 2009 (143), Jeong, *et al*. 2010 (119), Kang, *et al*. 2010 (120), Hwang, *et al*. 2011 (123), Jeong, *et al*. 2011 (124), Maeda, *et al*. 2011 (125), Ono, *et al.* 2011 (126), Park, *et al.* 2011 (127), Yamamoto, *et al.* 2011 (129), Kim, *et al.* 2012 (133), Tang, *et al.* 2012 (135), Wu, *et al.* 2012 (136), Zou, *et al.* 2012 (137)	High
Clinical	*CYP2C19*3* (and possibly other loss-of-function alleles) is associated with adverse cardiovascular outcomes (e.g., cardiovascular death, myocardial infarction, stroke, stent thrombosis) in ACS/PCI patients treated with clopidogrel.	Collet, *et al.* 2009 (28), Mega, *et al.* 2009 (2), Simon, *et al.* 2009 (5), Harmsze, *et al*. 2010 (139), Jeong, *et al*. 2011 (124), Yamamoto, *et al.* 2011 (129), Wu, *et al.* 2012 (136), Zou, *et al.* 2012 (137)	High
Clinical	*CYP2C19*17* is associated with lower on-treatment platelet reactivity (pharmacodynamics) in ACS/PCI patients treated with clopidogrel.	Frere, *et al*. 2009 (144), Sibbing, *et al*. 2010 (29), Sibbing, *et al*. 2010 (106), Harmsze, *et al.* 2012 (131),	Moderate

		Li, *et al*. 2012 (35), Sorich, *et al*. 2012 (37), Subraja, *et al*. 2012 (145)	
Clinical	*CYP2C19*17* is associated with enhanced clopidogrel response and an increased bleeding risk in ACS/PCI patients treated with clopidogrel.	Sibbing, *et al*. 2010 (29), Tiroch, *et al*. 2010 (146), Harmsze, *et al.* 2012 (131), Li, *et al*. 2012 (35), Sorich, *et al*. 2012 (37)	Moderate
Clinical	*CYP2C19* loss-of-function alleles are not associated with adverse cardiovascular outcomes in coronary patients with low frequencies of PCI and with other indications (e.g., atrial fibrillation) treated with clopidogrel.	Pare, *et al*. 2010 (88), Wallentin, *et al*. 2010 (9)	High
Clinical	ACS/PCI patients with *CYP2C19* reduced metabolizer genotypes have reduced risks of primary outcome with prasugrel compared to clopidogrel. However, for *CYP2C19* EMs, the risks with prasugrel and clopidogrel are not significantly different.	Sorich, *et al*. 2010 (147)	High
Clinical	ACS/PCI patients with *CYP2C19* reduced metabolizer genotypes have reduced risks of primary outcome with ticagrelor compared to clopidogrel, which was less significant among *CYP2C19* EMs and most pronounced among patients undergoing PCI.	Wallentin, *et al*. 2010 (9), Hulot, *et al*. 2011 (90)	High

ACS: acute coronary syndrome; EM: extensive metabolizer; PCI: percutaneous coronary intervention
* See above for description of '**Levels of Evidence Linking Genotype to Phenotype**'.

Supplemental Table S7. Evidence linking *CYP2C19* genotype with clopidogrel response (META-ANALYSES)

Study Design	Study Inclusion Date	Significant *CYP2C19* Genotype Risk	References
Meta-analysis of *CYP2C19*2* and PPI: - 10 studies - 11,959 total patients - established CAD	October 2009	**MACE:** **2* carrier: OR: 1.29 (1.12-1.49) **ST:** **2* carrier: OR: 3.45 (2.14-5.57) Heterozygotes: OR: 3.34 (1.84-5.93) Homozygotes: OR: 4.68 (1.55-14.11)	Hulot, *et al*. 2010 (6)
Meta-analysis of *CYP2C19*2*: - 8 studies - 8,280 total patients - established CAD undergoing PCI	December 2009	**MACE:** **2* carrier: OR: 1.46 (1.01-2.13) **Cardiac mortality:** **2* carrier: OR: 2.07 (1.22–3.52) **MI:** **2* carrier: OR: 1.69 (1.09-2.61) **ST:** **2* carrier: OR: 3.81 (2.27-6.40) **Ischemic stroke:** **2* carrier: OR: 5.78 (1.62-20.65)	Jin, *et al*. 2011 (148)
Meta-analysis of *CYP2C19*2*: - 7 studies - 8,043 total patients - established CAD	January 2010	**MACE:** **2* carrier: RR: 1.96 (1.14-3.37) **ST:** **2* carrier: RR: 3.82 (2.23-6.54)	Sofi, *et al*. 2011 (86)
Meta-analysis of *CYP2C19* LOF alleles: - 9 studies - 9,685 total patients - established CAD (91% PCI)	August 2010	**MACE:** Heterozygotes: HR: 1.55 (1.11-2.17) Homozygotes: HR: 1.76 (1.24-2.50) **ST:** Heterozygotes: HR: 2.67 (1.69-4.22) Homozygotes: HR: 3.97 (1.75-9.02)	Mega, *et al*. 2010 (7)
Meta-analysis of *CYP2C19* LOF and GOF alleles: - 11 studies (for *CYP2C19* loss-of-function alleles)	October 2010	**MACE:** **2* carrier: Not significant.	Zabalza, *et al.* 2012 (149)

- 16,360 total patients (for *CYP2C19* loss-of-function alleles) - CAD and others		**17* carrier: HR: 0.75 (0.66-0.87) **ST:** **2* carrier: HR: 2.24 (1.52-3.30) **Major bleeding:** **17* carrier: HR: 1.26 (1.05-1.50)	
Meta-analysis of *CYP2C19* LOF and GOF alleles: - 12 studies - 18,529 total patients - established CAD	December 2010	**MACE:** LOF carrier: Not significant. **ST:** LOF carrier: OR: 1.77 (1.31-2.40)	Bauer, *et al.* 2011 (150)
Meta-analysis of *CYP2C19* LOF alleles: - 16 studies - 20,785 total patients - established CAD	September 2011	**MACE:** **2* carrier: OR: 1.42 (1.13-1.78) Heterozygotes: OR: 1.43 (0.93-2.19) Homozygotes: OR: 1.75 (1.23-2.51) **Cardiac mortality:** **2* carrier: OR: 2.18 (1.37–3.47) **MI:** **2* carrier: OR: 1.42 (1.12-1.81) **ST:** **2* carrier: OR: 2.41 (1.76-3.30)	Jang, *et al.* 2012 (151)
Meta-analysis of *CYP2C19* LOF and GOF alleles: - 32 studies - 42,016 total patients - unselected	October 2011	**MACE:** LOF carrier: Not significant. **Stent thrombosis:** LOF carrier: RR: 1.75 (1.50-2.03)	Holmes, *et al.* 2011 (89)
Meta-analysis of *CYP2C19*2* and VerifyNow® platelet testing: - 7 studies (for *CYP2C19*) - 5,307 total patients (for *CYP2C19*) - established CAD	October 2011	**MACE:** **2* carrier: Not significant. **Stent thrombosis:** **2* carrier: OR: 2.65 (1.46-4.84)	Yamaguchi, *et al.* 2012 (152)
Meta-analysis of *CYP2C19*2* and *ABCB1* c.3435C>T: - 14 studies - 19,601 total patients		**MACE:** **2* carrier: RR: 1.28 (1.06-1.54) **Cardiac mortality:** **2* carrier: RR: 3.21 (1.65–6.23)	Singh, *et al.* 2012 (153)

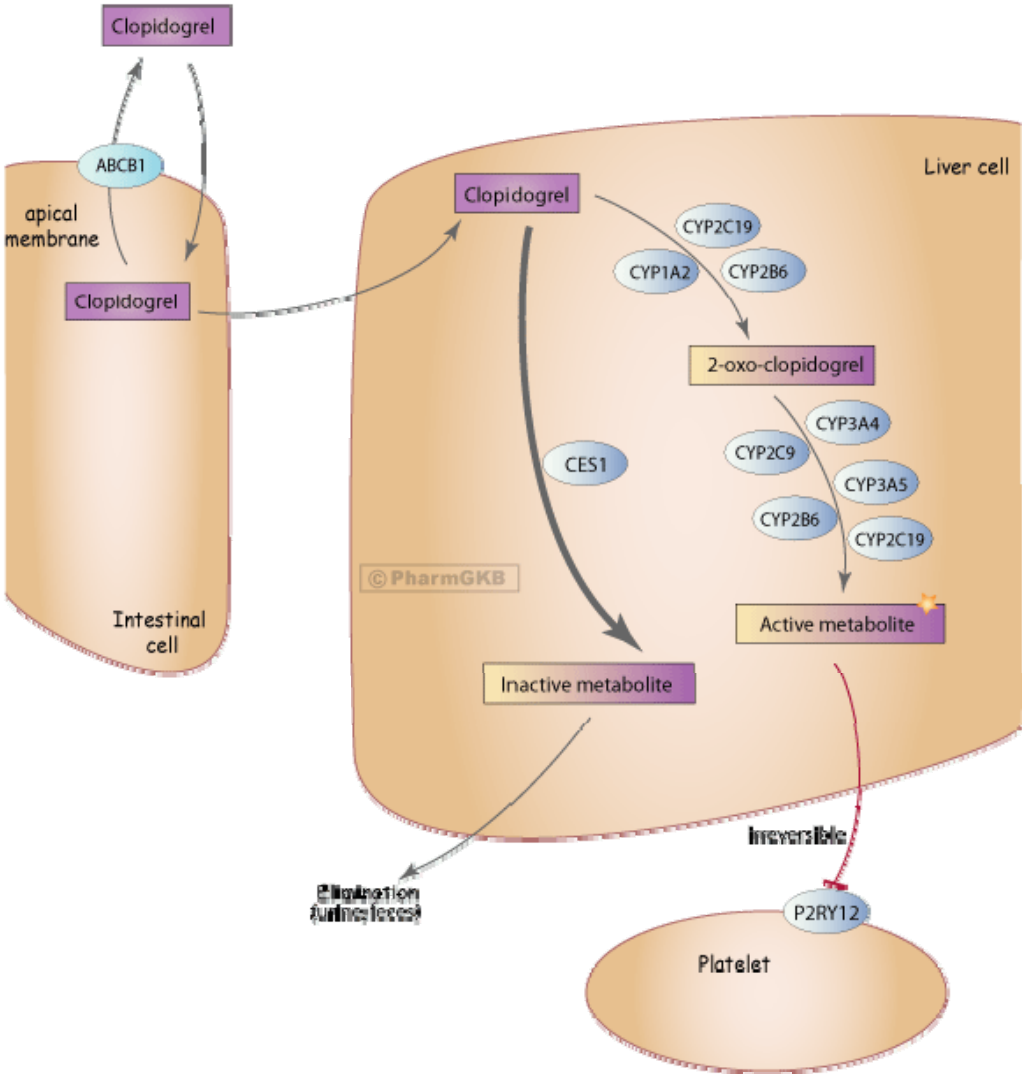
- established CAD		**MI:** **2* carrier: RR: 1.36 (1.12-1.65) **ST:** **2* carrier: RR: 2.41 (1.69-3.41)	

CAD: coronary artery disease; GOF: gain-of-function; HR: hazard ratio; LOF: loss-of-function; MACE: major adverse cardiovascular event; MI: myocardial infarction; OR: odds ratio; PPI: proton pump inhibitor; RR: relative risk; ST: stent thrombosis.
* See above for description of '**Levels of Evidence Linking Genotype to Phenotype**'.

Supplemental Table S8. Evidence linking *CYP2C19* genotype with phenotype (CLOPIDOGREL DOSE ESCALATION)

Study Endpoints	Major Findings	References	Level of Evidence*
Ex vivo platelet aggregation	Higher-dose clopidogrel can increase the degree of platelet inhibition in healthy subjects heterozygous for *CYP2C19* LOF alleles	Simon, *et al*. 2011 (57)	High
Ex vivo platelet aggregation	Higher-dose clopidogrel can increase the degree of platelet inhibition in patients heterozygous for *CYP2C19* LOF alleles but less so in patients homozygous for LOF alleles	Gladding, *et al*. 2008 (154), Gladding, *et al*. 2009 (40), Barker, *et al*. 2010 (155), Bonello, *et al*. 2010 (156), Alexopoulos, *et al*, 2011 (157), Collet, *et al*. 2011 (114), Cuisset, *et al*. 2011 (122), Mega, *et al*. 2011 (158)	High
Clinical: composite end point of cardiovascular death, MI and ST	Higher dose clopidogrel on the basis of platelet function monitoring does not result in clinical benefit among ACS/PCI patients.	Price, *et al*. 2011 (159), Collet, *et al*. 2012 (160)	High

ACS: acute coronary syndrome; LOF: loss-of-function; PCI: percutaneous coronary intervention.
* See above for description of '**Levels of Evidence Linking Genotype to Phenotype**'



Supplemental Figure S1. Hepatic metabolism of clopidogrel (161). For a detailed and updated description, see: http://www.pharmgkb.org/do/serve?objId=PA154424674&objCls=Pathway. Reproduced with permission by PharmGKB and Stanford University.

References

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