UNC HEALTH CARE

MEMORANDUM #11

TO: UNC Hospitals Attending Physicians, Housestaff, Department Heads, Nursing Coordinators, Nursing Staff, Supervisors, Inpatient Pharmacy Services

FROM: Karen Weck, M.D., Director of Molecular Genetics Laboratory KW
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DATE: April 14, 2010

SUBJECT: New Test: CYP2C19 genotyping to detect resistance to clopidogrel

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The UNC Molecular genetics laboratory is pleased to announce a new test to detect *cytochrome P450 2C19 (CYP2C19)* sequence variants associated with resistance to clopidogrel (Plavix) anti-platelet therapy and increased cardiovascular morbidity and mortality.

Clopidogrel is an anti-platelet agent used to treat coronary artery disease, peripheral vascular disease and cerebrovascular disease. A significant proportion of patients are at risk for myocardial infarction, stent thrombosis, or stroke due to insufficient clopidogrel-induced platelet inhibition. Clopidogrel is metabolized by CYP2C19 and other liver enzymes to an active form. Genetic variants of *CYP2C19* associated with altered CYP2C19 activity have been identified and are relatively common in most populations. Individuals with loss of function variants CYP2C19*2 or CYP2C19*3 (~15% of the population) are at increased risk for thrombotic cardiovascular events due to decreased drug efficacy. High risk populations include patients with recent acute coronary syndrome, coronary stent implantation and previous stroke. In contrast, the fast (ultra)-metabolizing variant CYP2C19*17 (in ~20% of the population) is associated with increased drug activation and increased risk of bleeding.

The US FDA has recently recommended considering a higher dose of clopidogrel or using alternative therapy such as prasugrel in CYP2C19 poor metabolizers who are homozygous for loss of function alleles (CYP2C19*2 or CYP2C19*3). Testing is recommended in patients who are being considered for clopidogrel antiplatelet therapy or who are already on this medication. The Division of Cardiology can be consulted regarding clinical use of this genetic test.

A clinical trial led by the Division of Cardiology is ongoing at UNC Hospitals to further optimize medical management in patients with *CYP2C19* poor metabolizing genetic variants. Contact Joseph Rossi, MD, or Jaya Dharmavaram, MD at 919-843-5215 for further information.

The CYP2C19 genotyping assay will be run twice a week. The preferred sample is 2mL of EDTA anticoagulated blood (lavender-top), which may be refrigerated up to 48 hours. Genomic DNA is extracted and CYP2C19 *2, *3 and *17 are detected by a TaqMan allelic discrimination genotyping assay. Homozygous or heterozygous presence of the three *CYP2C19* variants (*2, *3, *17) is reported.

References:

Shuldiner AR, et al. Association of cytochrome P450 2C19 genotype with the antiplatelet effect and clinical efficacy of clopidogrel therapy. JAMA 2009;302(8):849-57.

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Mega JL, et al. Cytochrome p-450 polymorphisms and response to clopidogrel. N Engl J Med 2009;360(4):354-62.

Simon T, et al; French Registry of Acute ST-Elevation and Non-ST-Elevation Myocardial Infarction (FAST-MI) Investigators. Genetic determinants of response to clopidogrel and cardiovascular events. N Engl J Med 2009;360(4):363-75.

Sibbing D, et al. Cytochrome 2C19*17 allelic variant, platelet aggregation, bleeding events, and stent thrombosis in clopidogrel-treated patients with coronary stent placement. Circulation. 2010;121(4):512-8.

Questions? Call the **Molecular Genetics Lab** at **(919) 966-4408** or email Dr. Karen Weck at: kweck@unch.unc.edu. For more information, see our website: http://labs.unchealthcare.org/directory/molecular_pathology/index_html