Meeting Report

AAPS–FIP Summary Workshop Report: Pharmacogenetics in Individualized Medicine: Methods, Regulatory, and Clinical Applications

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Abstract. The workshop “Pharmacogenetics in Individualized Medicine: Methods, Regulatory, and Clinical Applications” was held November 15–16, 2008 in Atlanta, Georgia, USA. This workshop provided an opportunity for pharmaceutical scientists, clinical practitioners, clinical laboratory scientists, and FDA to discuss methods, regulatory, and the application of pharmacogenetics in clinical practice and drug discovery. Key highlights of the workshop were: (a) the use of genetic information in individualized medicine has significant potential in advancing drug development and human health by optimizing drug response, drug efficacy, and preventing adverse drug reactions; (b) various barriers exist preventing the advance of the individualized medicine in the society, industry, and clinical practice; and (c) the barriers may be overcome by integrated approaches; the education of researchers, clinical practitioners, and patients and fostering interactive communication among stakeholders. By targeting the AAPS audience, this workshop was one step among many steps that AAPS–FIP is intending to take towards removing the barriers to widespread uptake of pharmacogenetics in drug discovery and clinical practice.

KEY WORDS: clinical pharmacology; drug discovery; drug metabolism; individualized medicine; pharmacogenetics; pharmacogenomics.

This report provides a summary of the workshop “Pharmacogenetics in Individualized Medicine: Methods, Regulatory, and Clinical Applications” co-sponsored by American Association of Pharmaceutical Scientists (AAPS) and the International Pharmaceutical Federation (FIP) held at Georgia World Congress Center, Atlanta, Georgia USA, November 15–16, 2008. The workshop was organized into three sessions of: (1) Introduction, Methods,

and Technology; (2) Clinical Applications; and (3) Industry, Regulatory, and Ethical Issues.

Goals and objectives of the workshop were: (1) to assess the importance of pharmacogenomics (PGx) in future drug therapy and diagnostics; (2) to discuss the enzyme classes responsible for drug metabolism and transport, and their functional variants associated with drug resistance or toxicity; (3) to evaluate the genetics of drug targets affecting drug pharmacodynamics, and how this may modulate treatment outcome or lead to drug resistance or toxicity; (4) identify new clinical applications for pharmacogenomics testing in cancer, cardiovascular, and drug adverse reactions; (5) review the complementary roles of traditional functional tests and genotyping in the clinical laboratory; (6) learn about SNPs and gene expression technology and the current technology available for pharmacogenetic testing; (7) review the current industry and regulatory perspectives on PGx; and (8) discuss the barriers to widespread uptake of individualized medicine.

The first session provided an overview of pharmacogenetics, methods, and technologies that are used in pharmacogenetics testing. Majid Moridani presented an overview of the PGx, followed by presentations on specific drugs and drug metabolizing enzymes responsible for the metabolism of tolbutamide (CYP2C9), omeprazole (CYP2C19), codeine (CYP2D6), 6-mercaptopurine (TPMT), irinotecan (UGT1A1), and isoniazid (NAT) polymorphisms. The influence of the genetic variants on efficacy and toxicity of these drugs were discussed to illustrate the benefits of genotyping in drug therapy and development of new drugs to optimize patient outcome and minimize adverse drug reactions. The second presenter, Steven Wong indicated that blood is usually

Opinions expressed in this report are those of the authors (Workshop Planning Committee) and do not necessarily reflect the views or policies of the FDA.

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the sample of choice, with buccal swap/oral fluid increasingly used in molecular/pharmacogenetic analysis. Based on a recent survey, the top ten genes subject to pharmacogenetic tests are: *CYP2D6*, *TPMT*, *CYP2C9*, *CYP2C19*, *NAT*, *CYP3A5*, *UGT1A1*, *MDR1*, *CYP2B6*, and *MTHFR*, updated with the addition of *VKORC1* and *CYP4F2*. The majority of these tests involve identifications of SNPs, gene deletion and duplication, with limited use of gene expression. By using the target amplification approach, DNA polymorphisms might be detected by the use of length analysis such as RFLP and oligomer ligase assays, sequencing, real-time PCR detection, PCR arrays, or fluorescence-based detection using beads. New developments would include signal amplification detection such as the FDA approved Invader assay for *UGT1A1* and Verigene using nanotechnology. As new technology is enabling point-of-care testing (POC) in laboratory medicine, POC molecular testing is rapidly developing, shortening turn-around-time, making it possible for physicians to have the information before prescribing the drugs. The next speaker, Wolfgang Sadec provided a brief outline of current and emerging methods used to find functional polymorphisms relevant to disease and drug response. He gave several examples for the discovery of functional polymorphisms with an ever increasing spectrum of methods (traditional genetic methods applicable to candidate genes, clinical genome-wide association studies (GWAS), mRNA profiling with GWAS, and ultra-high throughput sequencing). His presentation then focused on the detection of polymorphisms in regulatory regions of the genes because these are now considered a dominant factor in human evolution and interindividual variability. Sadec discussed the detection of allelic mRNA expression and processing, followed by SNP scanning for finding the responsible variants. He illustrated how this approach can detect novel genetic variants that have been missed by intense previous study. Validated functional genetic variants in critical candidate genes can then be tested for phenotypic impact in clinical studies, eventually leading to novel biomarker tests, or improving existing ones. The next presenter, David Cole, emphasized that although simple in concept, molecular medicine is not so simple in clinical practice. He predicted that technologic advances now allow us to identify so many genetic variants affecting such a wide variety of drugs that pharmacogenetics is on the verge of becoming part of routine practice, at least in the clinical laboratory. He discussed the Toronto experience with three different tests: HLA-B*5701 testing for abacavir hypersensitivity, TPMT testing for azathioprine sensitivity, and multiple variant testing for warfarin sensitivity and resistance demonstrating the benefit of using genetic information in the management of patient in a clinical setting.

In the second session, the impact of pharmacogenetics in four therapeutic areas was discussed. Daniel Hayes highlighted the importance of pharmacogenetics in oncology with an emphasis on breast cancer therapy. Numerous recent research findings have highlighted the importance of the cancer tissue characteristics such as estrogen receptor and HER2 content. Several examples of the potential benefit of germ-line as well as tumor genotyping have now been demonstrated. Furthermore, the Consortium of Breast Cancer Pharmacogenomics (COBRA) has shown that the metabolism of the pro-drug tamoxifen is totally dependent on *CYP2D6*. He concluded that preliminary data suggest that patients homozygous for inactivated *CYP2D6* alleles or those taking inactivating concurrent medications have a worse outcome on tamoxifen therapy. The next presenter, Anke-Hilse Maitland-van der Zee, discussed the problems associated with pharmacogenetic study of

cardiovascular disease. She indicated that one of the main problems in pharmacogenetic/genomic research is that many findings of the reported drug-gene interactions cannot be replicated in other populations. This is probably due to the fact that for a large number of drugs, especially for drugs used in multifactorial diseases such as cardiovascular disease, not just one gene but many genes are important in the explanation of the efficacy or side-effects of drugs. Therefore, it is important to obtain more insight into the molecular and genetic mechanisms of drug action. If the biological pathways involved are known, multiple genes in these pathways should be investigated. For pharmacogenetic research this means that large study populations are needed, and that many candidate genes (or genome wide screens) should be genotyped. Next, Ann Daly discussed the pharmacogenetics of drug targets using warfarin as an example. She mentioned that *CYP2C9* and *VKORC1* are now known to affect dose requirements of warfarin. A number of independent studies have shown that 50% of individual warfarin dose requirement is determined by the *CYP2C9* and *VKORC1* genotypes. Two clinical trials are planned to be started soon in the USA and Europe that will hopefully answer the question whether *CYP2C9* and *VKORC1* genotyping before warfarin therapy will lead to clinical benefits. The last speaker of the session was Vicki Ellingrod who discussed the pharmacogenetics of adverse drug reactions in psychiatry. She indicated that despite the effectiveness of currently available antipsychotics, use of second generation agents (eg. olanzapine, risperidone) are associated with metabolic disturbances such as weight gain, insulin resistance, diabetes mellitus, and the metabolic syndrome. In addition to an increased risk for cardiovascular disease, presence of these adverse drug reactions increases the risk of non-compliance. Therefore, it is of utmost importance to identify clinically useful markers for those at high risk for these adverse events. The serotonin 2C receptor (*HTR2CR*), leptin gene (*LEP*), leptin receptor (*LEPR*), methylenetetrahydrofolate reductase (*MTHFR*), and brain-derived neurotrophic factor (*BDNF*) have all implicated to have a role in the development of these metabolic complications. The conclusion of this session was that much interesting research in pharmacogenetics is appearing in the literature and being applied to clinical problems. Several gene-drug interactions are currently under investigation for clinical implementation. Importantly, pharmacogenetics is starting to find its way into clinical practice.

The last session of the workshop on the second day included five lectures with various discussions from the multiple viewpoints covering industry, regulatory, and ethical perspectives. Daniel Nebert stated that sequencing of the entire human genome, the mapping of common haplotypes of single-nucleotide polymorphisms (HapMap), and cost-effective genotyping technologies leading to genome-wide association (GWA) studies have demonstrated the requirements needed to separate true associations from the plethora of false positives. Continuous discoveries of new surprises about our genome cause us to question reviews declaring that "personalized medicine is almost here" or that "individualized drug therapy will soon be a reality". There are dozens of reasons why an "unequivocal genotype" or even an "unequivocal phenotype" is virtually impossible to achieve in current limited-size studies of human populations. This problem (of insufficiently stringent criteria) leads to decreased statistical power and, consequently, equivocal interpretation of most genotype-phenotype association studies. We must appreciate that all drug responses are gradients; accordingly, he predicts that the future

of individualized drug therapy will involve a combination of genomics, metabonomics, and proteomics rather than by DNA tests alone. Eric Stanek focused on the perspectives of pharmaceutical industry, employers/payers, and health/pharmacy benefit managers. The pharmaceutical industry may be able to streamline the drug development by pharmacogenomics. Conversely, this approach may also serve to limit market potential, add regulatory complexity, or diminish competitiveness. It was also demonstrated that pharmacy benefit managers was in the unique position to research and apply personalized medicine. The next speaker, Ross McKinnon, pointed out the various problems of the individualized medicine for clinical settings and expected the implementation of the individualized medicine in 2018. He mentioned that an increasingly complex series of barriers must be overcome if we are to successfully harness profiling advances for widespread implementation in the clinical setting. Some of these potential barriers are relatively well-defined and include difficulties around study design and genotype/phenotype correlations. He also highlighted in his talk some of the other challenges such as complex issues around workforce education, economic models for implementation, practice change, professional boundaries, and a vast array of social and ethical issues. The next speaker from the FDA, Gilbert Burchart, overviewed the utilization of FDA label information on genomic biomarkers and the factors which determine the incorporation of medical innovation. He focused on the legitimacy required for individualized medicine. Pharma-

cogenetics should be validated, be cost-effective, be accepted by medical practitioners, and have a stable public policy supporting it before it can be implemented in clinical practice. Hitoshi Sasaki summarized the discussion on various aspects of the workshop on individualized medicine. Genetic information is not sufficient for the implementation of individualized medicine because the gene cannot alone reflect the present dynamics in drug response (efficacy, toxicity, and pharmacokinetics). Personalized medicine will be achieved by integrated approaches of molecular diagnosis, molecular imaging, informative technology, and the use of several data banks for genotype and phenotype. Finally, Vinod P. Shah, FIP Scientific Secretary, gave the participants and speakers closing remarks with appreciation.

The conclusion of the workshop was that the use of genetic information in individualized medicine has significant potential in advancing drug development and human health by optimizing drug response, drug efficacy, and preventing adverse drug reactions. The workshop discussed various barriers preventing the advance of the individualized medicine in the society, industry, and clinical practice. The barriers may be overcome by integrated approaches; the education of researchers, clinical practitioners, and patients and fostering interactive communication among stakeholders. By targeting the AAPS audience, this workshop was one step among many steps that AAPS-FIP is intending to take towards removing the barriers to widespread use of pharmacogenetics in drug discovery and clinical practice.