Pharmacogenomics: a scientific revolution in pharmaceutical sciences and pharmacy practice
Report of the 2001/02 Academic Affairs Committee

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According to the Bylaws of the AACP, the Academic Affairs Committee shall consider

the intellectual, social, and personal aspects of pharmaceutical education. It is expected to identify practices, procedures, and guidelines that will aid faculties in developing students to their maximum potential. It will also be concerned with curriculum analysis, development, and evaluation beginning with the preprofessional level and extending through professional and graduate education. The Committee shall seek to identify issues and problems affecting the administrative and financial aspects of member institutions. The Academic Affairs Committee shall extend its attention beyond intra-institutional matters of colleges of pharmacy to include interdisciplinary concerns with the communities of higher education and especially with those elements concerned with health education.

In an effort to prepare academic pharmacy to anticipate and respond to the impact of the emerging knowledge of pharmacogenetics, pharmacogenomics, proteomics, and bioinformatics on the future roles of pharmacists, President Milap C. Nahata asked the 2001/02 AACP Academic Affairs Committee to:

- Discuss how pharmaceutical education might respond in light of this evolving knowledge base and meet the needs of the profession, health care system, and society;
- Identify curricular outcomes, instructional strategies, faculty development needs and strategies, and resource implications; and
- Develop a series of recommendations for the Association to guide academic institutions, educational programs, and faculty so they may prepare students with the necessary abilities for their future practice.
Background

It is well recognized that patients respond differently to the same medication, and such differences in drug toxicity or efficacy are often much greater across a population of patients than between monozygotic twins. This suggests that some of the inter-patient variability in drug efficacy and/or toxicity is related to inherited differences in genes that control drug disposition and effects in humans. There are now numerous examples establishing that such inter-individual differences can be attributed, at least in part, to polymorphisms in genes encoding drug metabolizing enzymes, drug transporters, and/or drug targets (e.g., receptors, enzymes). It is also clear that many non-genetic factors influence the effects of medications in patients, including the nature and severity of the disease being treated and the individual’s age, race, organ function, concomitant therapy, drug interactions, and concomitant illnesses. Pharmacists and pharmaceutical scientists have played a key role in deciphering these determinants of drug behavior in man and translating this knowledge to optimize pharmacotherapy in patients. While these non-genetic factors are often very important, inherited differences in the way individuals metabolize and eliminate drugs and genetic polymorphisms in the targets of drug therapy (e.g., receptors) can have an even greater influence on the efficacy and toxicity of medications.

Pharmacogenomics is a burgeoning field that seeks to describe the genetic basis for inter-individual differences in drug efficacy and toxicity, using genome-wide approaches to identify genes that govern an individual’s response to specific medications. As the initial draft of the human genome has revealed, there are over 1.4 million single nucleotide polymorphisms (SNPs) in the human genome, with over 60,000 of these residing in the coding regions of human genes. Some of these SNPs have already been associated with significant changes in the metabolism or effects of commonly used medications. For some genetic polymorphisms (e.g., thiopurine S-methyltransferase [TPMT], CYP2D6, N-acetyltransferase), monogenic traits have a marked effect on pharmacokinetics, such that individuals who inherit an enzyme deficiency must be treated with substantially different doses of the affected medications (e.g., five to ten percent of the standard mercaptopurine dose in patients inheriting two mutant allele for TPMT). Likewise, polymorphisms in drug targets (e.g., beta adrenergic receptor) have been shown to alter the sensitivity of patients to treatment with medications that target these receptors (e.g., beta-agonists), changing the pharmacodynamics of drug response. Because most drug effects are determined by the interplay of several gene products that govern the pharmacokinetics and pharmacodynamics of medications, pharmacogenomics research is increasingly focused on understanding these polygenic determinants of drug effects.

The potential importance of pharmacogenetics is not new: clinical observations of inherited differences in drug effects were first documented in the 1950’s (1-3) giving rise to the field. Pharmacogenetics has now been rediscovered by the pharmaceutical industry and a broader spectrum of academia, giving birth to pharmacogenomics. Although the two terms are often used interchangeably, pharmacogenomics is used herein to describe the genome-wide approach to identifying genes that govern an individual’s response to drug therapy. The molecular genetic basis for inherited differences in drug metabolism began to be elucidated in the late 1980’s, with the initial cloning of a polymorphic human gene encoding the drug metabolizing enzyme debrisoquin hydroxylase (CYP2D6). The human genes involved in many such pharmacogenetic traits have now been isolated, with their molecular mechanisms and clinical importance more clearly defined. The ultimate goal of pharmacogenomics is to define the contributions of inherited differences in drug disposition and/or targets to drug response, and thereby improve the safety and efficacy of medications through the use of genetically guided, individualized treatment. As the molecular mechanisms of pharmacologic effects, genetic determinants of disease pathogenesis, and polymorphisms in genes that govern drug metabolism and disposition are better understood, these polygenic determinants become more tractable. More sophisticated molecular tools are available for detection of gene polymorphisms. Advances in bioinformatics help us assess which of these genetic determinants are useful.
in developing a more rational, individualized drug therapy (4,5). Such knowledge should make it possible to select drug therapy based on each patient’s inherited ability to metabolize, eliminate, and respond to specific medications, providing a powerful scientific foundation for optimizing pharmacotherapy.

How will pharmacogenomics change the practice of pharmacy?

The potential is enormous for pharmacogenomics to yield a powerful set of molecular diagnostics that will become routine tools by which pharmacists and physicians select the proper medications and doses for each individual patient. Instead of starting patients on the “average dose” that was found to be safe and effective in most patients in large clinical trials, pharmacogenomics has the potential to provide patient-specific data upon which the selection of medications and doses can be individualized and optimized. Unlike a serum creatinine to measure renal function, or serum bilirubin to assess liver function, or essentially all other biochemical tests, a patient’s genotype for any given gene only needs to be determined once because it does not change over time. Using the amount of DNA that can be isolated from just 10 milliliters of blood, it is possible to determine thousands of genotypes, even with current technology. Furthermore, technology is improving so rapidly that it will soon be possible to test for greater than 50,000 SNPs in one assay using DNA microarrays, or so called “DNA chips.” So, taken together, the process will be to collect a single blood sample from each patient, submit an aliquot of the sample to a reference laboratory for analysis of a panel of genotypes, and test for those established to be important determinants of drug disposition and effects. The results of this one panel of tests would be electronically deposited into a secured database, into and out of which data can be accessed only with the patient’s authorization (to her/his pharmacists, physicians, other health care professionals, and counselors). The results of these tests will not be simply a list of gene SNPs, but rather a report formatted and interpreted according to the patient’s diagnosis and treatment options. For example, the report could be a recommended algorithm for the selection of antihypertensives, starting with those most likely to be effective and well tolerated, based on the patient’s genotypes for the panel of genes known to be significant determinants of the disposition and effects of hypertension medications. As patients experience additional illnesses, additional genotypes will be characterized and the data added to the same secured database, to which the patient’s future physicians and pharmacists would be granted access as needed to make treatment decisions. Of course, these new tools will not replace the more conventional biochemical tests that are now routinely used to assess organ function and disease progression, rather they will complement these contemporary tests and provide additional tools for selecting medications that are optimal for each patient. Furthermore, genotyping will not obviate the need for follow-up assessment of response, adherence to treatment, or drug interactions, which will continue to be important clinical responsibilities of pharmacists. However, pharmacogenomics will make the practice of pharmacy and medicine less an art and more a science, thereby improving the efficacy and reducing the toxicity that results from pharmacotherapy.

Over what timeframe will we see the impact of pharmacogenomics on the practice of pharmacy?

The change is already underway, but will not likely be fully developed for a decade or more. There are currently known genotypes being used for the selection of medications and doses, and the number of important pharmacogenomic discoveries is increasing steadily. At present, these applications are limited largely to medications that have narrow therapeutic indices (e.g., anticancer medications), but as additional pharmacogenomic relationships are discovered, the number of applications will continue to grow. Fueling this burgeoning field are dozens of genomic companies, academic centers, and large pharmaceutical companies that are conducting studies to uncover and understand the genetic determinants of drug response. Furthermore, there are many biotechnology companies working to develop higher throughput and less expensive methods to determine genotypes. It has been estimated that the cost of genotyping is decreasing by a factor of two each year, so that by 2010 the cost of determining a patient’s entire genome sequence could be under $1000. If that were to be accomplished, then the paradigm could
be that a newborn’s entire genome sequence could be deposited in a secured database prior to the parents and new baby leaving the hospital. Thus, the greatest challenge before us is not the technology for determining a patient’s genotype (or haplotype), rather the challenge is deciphering the genetic determinants of drug response. With what is now estimated to be over 50,000 human genes, and over 1.4 million SNPs, the greatest challenge is to determine which combinations of these are important in determining the effects of medications in patients. This is the major task before us in the next decade, representing an extraordinary opportunity for pharmacists and pharmaceutical scientists to participate in the discovery of these pharmacogenomic traits and their application to clinical practice.

*How might pharmaceutical education respond in light of this evolving knowledge base and meet the needs of the profession, health care system, and society?*

Changes in the educational emphasis and biotechnology content in US colleges and schools of pharmacy have evolved over the past ten years following the recommendations expressed in the 1990 AACP White Paper, *The Impact of Biotechnology Upon Pharmacy Education* (6). Most of the instruction in preprofessional courses in biology has been modified considerably over that decade, with a systematic though still elementary treatment of genetics, genomics, and proteomics. As a result, frequent discussions compare human genes with homologous genes in *c-elegans, drosophilla* or in other organisms whose chromosomes have been nearly or completely mapped. As students progress through the pharmacy curriculum, there is a continuation of such discussions within biochemistry, medicinal chemistry, physiology, pathophysiology, pharmacology, and pharmacotherapy courses.

In the last ten years, advances in molecular biology and genetics have led to many changes in pharmaceutical education. The pharmaceutical industry has developed new protein biopharmaceuticals using recombinant DNA strategies, monoclonal-antibody-based therapeutics and diagnostics, antisense and other nucleotide therapeutics, and gene delivery strategies. These new kinds of products and applications have altered and will continue to alter pharmacotherapy. With developments in pharmacogenetics and pharmacogenomics, detailed information about specific regions of the human genome is available and the genetic basis for disease and success/failure of pharmacotherapy is being studied. All disciplines in the pharmacy curriculum will be affected to some degree by the increased understanding of the drug response through pharmacogenetics and pharmacogenomics. Pharmacy colleges and schools and practitioner organizations must play a central role in educating health professionals on how best to use the applications of advancing pharmacogenetic and pharmacogenomic research, and in articulating the role of pharmacists and pharmaceutical scientists in the development and use of gene-based therapies, as well as in making treatment choices as a result of available patient-specific genetic information.

**Curricular Outcomes and Instructional Strategies**

In January 2001, the National Coalition for Health Professional Education in Genetics (NCHPEG), of which AACP is a member, distributed to the health professions education community *Core Competencies in Genetics Essential for All Health-Care Professionals* (7), developed by a working group of specialists with broad experience in genetics and health professions. The document is available electronically at [http://www.nchpeg.org/news-box/corecompetencies000.html](http://www.nchpeg.org/news-box/corecompetencies000.html). The Academic Affairs Committee reviewed these competencies within the context of the emerging science and roles for pharmacists described earlier and provides a draft version of these competencies edited to be specific for pharmacists. These competencies are included in Appendix A.

**RECOMMENDATION 1:** AACP should reconvene the Center for the Advancement of Pharmaceutical Education (CAPE) Advisory Panel on Educational Outcomes to examine the *Educational Outcomes* to ensure that they maintain contemporary validity relative to roles and responsibilities of pharmacists and
requisite knowledge base, especially in within the emerging areas of pharmacogenomics and pharmacogenetics.

Faculty should use the curricular outcomes to revise course offerings and content and as a guide to determine instructional strategies appropriate to facilitate student achievement. An example strategy comes from the medical literature. Faculty in the Washington University School of Medicine developed a module using clinical cases to teach human genomics, bioinformatics, and problem-solving skills to first-year medical students (8). The module uses the databases available on the National Center for Biotechnology Information (NCBI) Web site and integrates genomics and bioinformatics content with introduction to technology and use of databases. The use of clinical cases as the platform for the module provides a practice relevant context for the outcomes addressed.

The National Center for Biotechnology Information is available at http://www.ncbi.nlm.nih.gov/Education/index.html. In addition to publicly accessible databases, the Web site offers educational resources such as introductions to bioinformatics, genome mapping, molecular modeling, SNPs, microarray technology, molecular genetics, pharmacogenomics, and phylogenetics and tutorials on how bioinformatics tools are used as a part of the research process and use of various databases.

Faculty Development Needs

The impact of pharmacogenetics, pharmacogenomics, and bioinformatics on health care, the practice of pharmacy, and the pharmaceutical sciences will be far-reaching, forever changing

- understanding of disease etiology and diagnosis,
- conceptual understanding of disease process and prognosis,
- understanding of determinants of drug effects,
- the nature and type of treatments available,
- how medications are packaged, dispensed, and administered,
- how medical literature, including databases, is accessed and used,
- approaches to drug therapy decision making and monitoring, and
- the nature of interaction between the pharmacist and patient.

As information continues to evolve, efficiencies in curriculum development, faculty development, and discovery will be gained from the collective effort of AACP individual and institutional members.

RECOMMENDATION 2: AACP should compile and maintain an online inventory of the activities at member institutions related to pharmacogenetics, pharmacogenomics, and bioinformatics, categorized into patient care/service activities; education, including professional degree programs and continuing professional education for practitioners; and research and graduate education.

RECOMMENDATION 3: The seven AACP academic sections should coordinate program planning for the 2003 AACP Annual Meeting to focus on the impact of pharmacogenetics, pharmacogenomics, and bioinformatics on their respective disciplines or combination of disciplines as appropriate. Programs should provide 1) primers on the foundational science, 2) opportunities to discuss impacts of that science on the pharmaceutical science research agenda, patient care practice, and pharmacy curriculum, and 3) a forum for sharing related activities of individual and institutional members.

References
APPENDIX A

Competencies in Pharmacogenetics and Pharmacogenomics for Pharmacists
derived, in part, from
Core Competencies in Genetics Essential for All Health-Care Professionals
National Coalition for Health Professional Education in Genetics (NCHPEG), January 2001

I. GENETIC BASIS OF DISEASE

A. KNOWLEDGE The pharmacist should understand:

1. basic genetic concepts and nomenclature
2. how identification of disease-associated genetic variations facilitates development of prevention and diagnostic strategies
3. the importance of family history (minimum three generations) in assessing predisposition to disease
4. the role of genetic factors in maintaining health and preventing disease
5. the difference between clinical diagnosis of disease and identification of genetic predisposition to disease (genetic variation is not strictly correlated with disease manifestation)
6. the role of behavioral, social, and environmental factors (lifestyle, socioeconomic factors, pollutants, etc.) to modify or influence genetics in the manifestation of disease
7. the role of appropriately credentialed genetics experts and peer support resources

B. SKILLS The pharmacist should be able to:

1. gather genetic family-history information, including an appropriate multigenerational family history
2. explain basic concepts of probability and disease susceptibility, and the influence of genetic factors in maintenance of health and development of disease
3. obtain credible, current information about genetics, for self, clients, and colleagues

C. ATTITUDES The pharmacist should:

1. seek coordination and collaboration with an interdisciplinary team of health professionals
2. recognize the limitations of his or her own genetics expertise
3. demonstrate willingness to update his or her own genetics knowledge at frequent intervals.

II. DRUG DISCOVERY AND DISPOSITION/DRUG TARGETS

A. KNOWLEDGE The pharmacist should:

1. recognize the large number of proteins that influence drug response, including drug transporters, drug metabolizing enzymes, direct protein targets of drugs and other proteins (e.g. signal transduction proteins) involved in the pharmacological effect.
2. appreciate the contribution of genetic variability to inter-individual variations in drug response
3. recognize the drugs/drug classes/clinical situations where pharmacogenetic testing is likely to be most useful clinically
4. understand how associations between genetic variations and drug response are investigated and uncovered
5. be able to identify important issues in pharmacogenetic study design, particularly those that differ from non-genetic clinical studies
6. know where/how to find pharmacogenetic information, including primary literature, databases, and other resources
7. understand that pharmacogenetic testing is like all other clinical testing – it will not have 100 percent reliability, but rather is used along with other clinical information
8. appreciate that pharmacogenetic testing may also reveal certain genetic disease predispositions (e.g. the Apo E4 polymorphism)
9. recognize the potential of behavioral, social, and environmental factors (lifestyle, socioeconomic factors, pollutants, etc.) to modify or influence genetics in the manifestation of disease
10. understand the influence (or lack thereof) of ethnicity in genetic polymorphisms and associations of polymorphisms with drug response
11. understand the potential physical and/or psychosocial benefits, limitations, and risks of pharmacogenetic information for individuals, family members, and communities
12. appreciate regulatory issues that may result from pharmacogenetics being incorporated into Phase II and III testing
13. understand the risks, benefits and options for a patient undergoing pharmacogenetic testing
14. be familiar with the resources available to assist clients seeking genetic information or services, including components of genetic-counseling and indications for referral to genetic specialists
15. appreciate the ethical, legal and social issues related to pharmacogenetic testing and recording of genetic information (e.g., privacy, the potential for genetic discrimination in health insurance and employment)
16. understand one’s own professional role in the referral to genetics services, or provision, follow-up, and quality review of pharmacogenetic tests

B. SKILLS  The pharmacist should be able to:

1. critically evaluate information obtained from pharmacogenetic/genomic clinical trials and identify limitations in study design, technology, and data interpretation that will influence patient care
2. identify the epidemiologic implications of pharmacogenetic/genomic studies and its impact at the societal level as well as that of the individual patient.
3. identify those patients in whom pharmacogenetic testing is indicated
4. identify the most appropriate pharmacogenetic test for a specific patient
5. effectively use information technologies, particularly databases, to obtain current information about pharmacogenetics
6. interpret the results of pharmacogenetic testing, and make drug therapy recommendations based on the results
7. identify drug therapy problems that may be related to genetic variability, even when a pharmacogenetic test has not been done
8. identify patients who have undergone pharmacogenetic testing in the past so that a specific test is not repeated unnecessarily
9. participate in professional and public education about pharmacogenetics
10. educate clients about availability of pharmacogenetic testing and the situations in which it is indicated
11. provide appropriate information about the potential risks, benefits, and limitations of pharmacogenetic testing
12. ensure that patients who are undergoing pharmacogenetic testing have undergone an appropriate informed consent process [Is this always required, even for a CLIA-certified test?]

13. provide, and encourage use of, culturally appropriate, user-friendly materials/media to convey information about genetic concepts and pharmacogenetic testing

14. discuss costs of pharmacogenetic services, benefits and potential risks of using health insurance for payment of pharmacogenetic services, including potential risks of discrimination

II. ETHICAL APPLICATIONS, SOCIAL AND ECONOMIC IMPLICATIONS

The pharmacist will:

1. support patient-focused policies.
2. understand the increased liability that accompanies access to detailed patient information.
3. maintain the confidentiality and security of patient health records.
4. be fair, impartial, personable, and accurate in the delivery of patient education.
5. tailor information and services to patient culture, education, and language.
6. be an outspoken advocate for patient rights.
7. adopt a code of conduct in patient treatment that is free of racial, ethnic, and religious bias.
8. adopt a culturally sensitive and ethical approach to patient counseling.
9. advocate against attempts to ascribe behavioral tendencies(social behavior) to patients on the basis of pharmacogenomic information.
10. employ clinical, humanistic, and economic outcomes research relative to pharmacogenomic interventions and services to insure appropriate and cost effective treatment of disease.
11. apply basic assessment and evaluation strategies to assess pharmacy-related services directed toward the provision of pharmacogenomic services and education developed for the individual patient and public at large.
12. interpret and apply public policy, including regulatory statements and issues, aimed at pharmacogenomic services and interventions.
13. participate in educational programs for the public as related to pharmacogenomic services and interventions.
14. identify appropriate resources offered by professional organizations, disciplines, or institutions.