

ACCP COMMENTARY

Recommended Basic Science Foundation Necessary to Prepare Pharmacists to Manage Personalized Pharmacotherapy

American College of Clinical Pharmacy

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Abstract

In recent years, the U.S. Food and Drug Administration has approved revised labeling for several existing drugs to include pharmacogenomic information, marking an important step toward more personalized medicine. In addition, it is anticipated that many newly approved drugs may be restricted to use in individuals with certain genotypes. In response to the wealth of pharmacogenetic data generated during the past decade and its implications for pharmacy practice, the American College of Clinical Pharmacy (ACCP) Educational Affairs Committee was charged with describing the basic science foundation necessary to prepare future pharmacists to manage personalized, pharmacogenetically driven therapy. The committee identified four key areas deemed essential components of the pharmacy curriculum related to advances in genomics: (1) personalized medicine concepts and terminology, with a focus on genomics; (2) genomic applications in basic and applied pharmaceutical sciences; (3) biotechnology; and (4) bioinformatics. Each section of this commentary contains one or more broad curricular outcomes to be achieved, suggested implementations to address each outcome, and benchmark performance indicators of learning outcomes for recent graduates from doctor of pharmacy educational programs. There was unanimous agreement among committee members that the curricular outcomes described are the minimum expectation for future pharmacists to provide optimal patient care in the era of personalized medicine. Material taught in each area should evolve with progress in the field, particularly for gene-drug response associations, biotechnology, and bioinformatics. As the areas of proteomics, metabolomics, and epigenetics evolve along with their implications for personalized drug therapy, they should also be incorporated into the curriculum. Self-directed learning behaviors should be encouraged, when possible, to better prepare students to advance their skills and knowledge with the science.

Faculty development will likely be necessary for the widespread education of pharmacy students in personalized medicine. It is our hope that this commentary will serve as a useful resource for academicians involved in curricular content development for pharmacy students.

Introduction

The American College of Clinical Pharmacy (ACCP) Educational Affairs Committee was charged with describing the basic science foundation necessary to prepare future pharmacists to manage personalized, pharmacogenetically driven therapy. As a precedent, one of the critical issues identified in ACCP's 2007–2012 Strategic Plan is, "How can ACCP increase its contribution to ensuring an appropriately educated and skilled clinical pharmacy workforce?"¹ The strategy for addressing this issue involves providing support for curricular content development and delivery in schools and colleges of pharmacy to better prepare the future clinical pharmacy workforce. The current committee charge is in response to the wealth of pharmacogenetic data generated during the past decade and the implications of these data on pharmacy practice.

Substantial interpatient variability exists in drug response. Hence, it is difficult to predict an individual's risk of adverse effects or likelihood of therapeutic benefit with a prescribed drug. Although clinical factors (e.g., age, comorbidities, concomitant therapy) are often considered when choosing drug therapy, these alone do not adequately predict drug response. It is now recognized that genetically determined differences in drug metabolism, drug distribution, disease-associated proteins, and drug target proteins play a major role in the observed interpatient variability in drug response.² In recent years, the U.S. Food and Drug Administration has approved revised labeling for several existing drugs (e.g., irinotecan, 6-mercaptopurine, warfarin, carbamazepine, phenytoin, abacavir, rasburicase) to include information on genetic variants linked to adverse drug effects or drug efficacy.³ Clinicians are awaiting clinical trial data on the use of genotype-informed prescribing for some drugs (e.g., warfarin, clopidogrel) before adopting pharmacogenomics in routine clinical practice.^{4,5} Nonetheless, the addition of genetic

information to product labeling marks a considerable step toward more personalized medicine. Similar to the prescribing recommendations for trastuzumab and cetuximab, several newly approved drugs may be restricted to use in individuals with certain genotypes. As experts in pharmacotherapy, pharmacists may well provide an increasingly valuable service in dealing with the complexities of the drug decision process in the era of personalized medicine.

Personalized medicine broadly refers to tailoring disease management on the basis of an individual's characteristics. In pharmacotherapy, personalized medicine involves basing drug therapy decisions on patient-specific factors such as clinical characteristics, genotype and gene expression, protein structure or function, and molecular profile. Pharmacogenomics, one component of personalized medicine, refers to the inherited basis for interindividual differences in drug response. The terms *pharmacogenomics* and *pharmacogenetics* are often used interchangeably. However, pharmacogenetics generally refers to a single gene influencing drug response, whereas pharmacogenomics refers to a combination of genes with effects on drug response. For simplicity, pharmacogenomics will be used to describe DNA sequence variation leading to alterations in drug response.

Proteomics, metabolomics, and epigenetics are other components of personalized medicine. Proteomics is the study of protein structure and function; metabolomics is the systemic analysis of biologic samples for small molecules (e.g., amino acids, carbohydrates, lipids, other organic compounds) generated by cellular processes.⁶ Protein function and molecular composition are dynamic and may change upon drug exposure. This is in contrast to an individual's DNA sequence, which remains consistent throughout life and may lead to predictable changes in pharmacokinetic and/or pharmacodynamic drug properties. Epigenetics refers to changes in gene function or expression that occur in the absence of DNA sequence

alterations because of mechanisms such as DNA methylation, histone modification, or the expression of regulatory noncoding RNAs.⁷

Pharmacy educators, practitioners, and regulators recognize the importance of addressing advances in personalized medicine and biotechnology in the pharmacy curricula.^{8,9} In particular, the Accreditation Council for Pharmacy Education (ACPE) identified the following elements as essential to the science foundation for the pharmacy curriculum in the 2007 ACPE Accreditation Standards and Guidelines.¹⁰

- “Genetic basis for disease and drug action
- Genetic basis for alteration of drug metabolism
- Genome and proteomic principles in relation to disease and drug development
- Genetic basis for individualizing drug doses
- Genetic basis for antibody synthesis, development, function, and immunopathology”

Both the American Association of Colleges of Pharmacy and the National Coalition for Health Professional Education in Genetics have provided guidance on particular curricular content deemed essential with respect to personalized medicine.^{9,11,12} Both organizations suggest core competencies to be achieved, focusing on the genomic component of personalized medicine, but neither provides suggestions for specific curricular changes to address these competencies.

In this commentary, we propose basic science curricular content essential for preparing doctor of pharmacy graduates entering practice to appropriately manage pharmacotherapy in the era of personalized medicine. The content described is aimed at providing basic education for all pharmacy students, recognizing that some graduates will have a larger role in personalized medicine, perhaps from a research, regulatory, or technology perspective, and will require further

education and training postgraduation. The application of metabolomics to predicting drug response is largely in its infancy and thus is not addressed to a large extent in this commentary. In addition, because protein function is largely under genetic control, this commentary will focus predominantly on genomic concepts. We wish to emphasize that personalized medicine also encompasses clinical factors, and clinicians should continue to consider these factors in drug therapy decisions. Hence, the content we recommend is meant to be integrated with existing curricula covering clinical variables that influence drug response. This commentary addresses four topics: personalized medicine concepts and terminology, with a focus on genomics; genomic applications in basic and applied pharmaceutical sciences; biotechnology; and bioinformatics. Each section contains one or more broad curricular outcomes to be achieved, suggested implementations to address each outcome, and benchmark performance indicators of learning outcomes for recent graduates from doctor of pharmacy educational programs. Although valuable, the ethical, social, legal, and economic ramifications of pharmacogenomic testing are believed to be beyond the scope of the basic science curricular content necessary to prepare graduates to manage personalized medicine; thus, they are not discussed.

Personalized Medicine Concepts and Terminology

- Curricular Outcome #1: Describe the structure of the human genome and alterations in the genome that can affect gene function and expression.
- Curricular Outcome #2: Describe the relevance of DNA sequence variants and alterations in gene function and expression to drug response.

Discussion

Genetics revolutionized the biologic sciences, launched molecular biology, and formed the basis of pharmacogenomics and epigenetics. As pharmacogenomics continues to progress from a basic to a clinical science, it will affect patient care on many levels. To optimize pharmacotherapeutic outcomes, pharmacists will need a broad understanding of human genetics and the potential consequences of gene modification on disease phenotype and drug response. To appropriately interpret pharmacogenomic data, pharmacists should have a strong foundation in molecular biology and biochemistry that is focused on the structure and function of DNA and RNA, chromosome packaging, the processes of gene transcription and translation, and the structure and expression of human genes.

Genotypic modifications are responsible for phenotypic differences in drug response through many mechanisms. Because of the important, dynamic nature of pharmacogenomics and epigenetics, pharmacists need a strong understanding of the types and consequences of genetic variation and alterations in gene function and expression. This includes a comprehension of single nucleotide polymorphisms (SNPs), which are currently understood to be responsible for most genetic polymorphisms; the clinical relevance and mechanisms of SNPs in the protein coding, promoter, and regulatory regions of the genome; intron and splicing SNPs; and SNPs in the untranslated regions of messenger RNA. Furthermore, pharmacists should have a basic understanding of the concepts of linkage disequilibrium and haplotype structure.

In addition to SNPs, pharmacists need a working knowledge of other types of DNA sequence variations, including multinucleotide insertions and deletions, microsatellites, polymorphisms of gene copy numbers, and variations caused by DNA substitution, inversion, translocation, and conversion. Pharmacists should also have an understanding of epigenetic mechanisms, including DNA methylation, histone modification, and expression of regulatory

noncoding RNA molecules (e.g., microRNAs). As pharmacogenomics and epigenetics evolve, personalized medicine will encompass synthesized information about variations in multiple genes across the genome to predict phenotypic effects. A multidisciplinary group, consisting of scientists and clinicians, will likely be required to store, manage, and, in some instances, decipher a large amount of genetic information for a particular patient. To be a valuable member of such a group, the pharmacist should show a thorough comprehension of the potential consequences of alterations in DNA structure and gene expression on protein function and possess the knowledge and skills to effectively communicate on these topics with members of the multidisciplinary group.

Suggested Implementation

Prerequisites for pharmacy education commonly include biology courses in which genome organization and gene expression are taught, and this prerequisite education should continue unchanged. A course in human genetics with a laboratory component should eventually be a prerequisite for entry in pharmacy school. Until fully implemented, coursework in genetics should be implemented in the pharmacy school curriculum for students without prior formal education in this area.

In addition to prerequisite or early preprofessional coursework in human genetics, students should receive specific instruction and training on genetic variations and the associated implications for protein function during their professional years of pharmacy school. Such material may be integrated into an existing curriculum or taught in courses specifically focused on pharmacogenomics and epigenetics.

Benchmark Performance Measures

- Pharmacy graduates will be able to describe various types of human genetic variation and genetic modifications leading to alterations in gene function and expression.
- Pharmacy graduates will be able to accurately predict the consequences of DNA sequence variation and epigenetic mechanisms on gene function, gene expression, protein structure, and protein function.

Genomic Applications in Basic and Applied Pharmaceutical Sciences

- Curricular Outcome #3: Describe the effects of DNA sequence variation and epigenetic mechanisms on human physiology.
- Curricular Outcome #4: Demonstrate proficiency in identifying genes and genetic variants with potential effects on drug response.
- Curricular Outcome #5: Predict the effects of variation in gene structure and expression on pharmacokinetics and pharmacodynamics.
- Curricular Outcome #6: Appropriately evaluate primary literature describing genetic association with drug therapy to assess its validity, limitations, and clinical significance.
- Curricular Outcome #7: Recognize and use online resources as sources of genetic information.

Discussion

The importance of genetic variation has expanded from its diagnostic value for inherited diseases to a tool for predicting physiologic differences and drug response. In addition to a fundamental knowledge of normal anatomy and physiology, an understanding of the genetic

influences of physiologic processes is essential for drug selection, dosing, use, and monitoring. Diuretic therapy may be especially effective for an individual with hypertension and a genotype predictive of excessive sodium reabsorption.¹³ However, amiodarone should be used with particular caution in patients with cardiac ion channel mutations that increase the risk of proarrhythmia.¹⁴ Thus, to appropriately apply genetic information to pharmacotherapy decisions, graduates must understand the relationship between genotype and phenotype.

Genetic variability can also affect drug pharmacokinetics and pharmacodynamics. In particular, genetic variation with an impact on drug-metabolizing enzymes, drug transporter proteins, and proteins at the drug target level can have profound effects on drug disposition and sensitivity, thereby influencing the likelihood of drug efficacy or risk of adverse effects.² To be effective members of a multidisciplinary group charged with incorporating genetic information into clinical practice, pharmacists must understand the effects of genetic variation on disease phenotype, pharmacokinetics, and pharmacodynamics. Graduates should also be knowledgeable about labeling recommendations and requirements regarding pharmacogenomic dosing, and they should have the ability to effectively interpret and appropriately apply such recommendations. Finally, basic skills in navigating and retrieving data from genetic databases will be valuable for fully characterizing drug effects on the basis of genetic information.

Suggested Implementation

Anatomy and physiology courses that are part of either the preprofessional or the early professional curriculum should focus not only on form (anatomy) and function (physiology), but also on the genetic control of each. Students should specifically be taught about common and relevant genetically associated alterations in human physiology. Pathophysiology courses offered

during the professional curriculum should emphasize the relationship between genotype and disease phenotype. Student exposure should include discussions of current and relevant clinical examples of genetically associated alterations in physiology and the resources needed to create individualized care plans for patients on the basis of their genetic information.

Courses in the pharmacologic sciences (e.g., medicinal chemistry, pharmacology, pharmacotherapy) should include instruction on genomic structure and function in relation to drug pharmacokinetics and pharmacodynamics. Concepts should be emphasized regarding drugs that act through genetic mechanisms and drugs whose concentrations and effects are influenced by genetic variation. Similar to discussions of genetic influences on human physiology, student discussions should include relevant clinical examples of genetically associated alterations in drug effects and the resources needed to create individualized care plans for patients on the basis of their genetic information. Such material may be integrated into an existing curriculum or taught in courses specifically focused on pharmacogenomics and epigenetics. Pharmacy curricula that include specific coursework in pharmacogenomics and epigenetics have an advantage in their ability to emphasize the growing importance of genetic information and individualization of drug therapy, but such curricula may not permit integrated application in other content areas (pharmacokinetics, pharmacology, therapeutics, etc.). Integrated courses have the benefit of closely incorporating pharmacogenomics and epigenetics into specific content areas (pharmacokinetics, pharmacology, therapeutics, etc.), but coverage may not be consistent.

Literature evaluation skills pertaining to genomics should also be incorporated into existing pharmacy curricula. In particular, students should gain experience in interpreting primary literature that focuses on pharmacogenomics, including the use of statistical tests common to genomic evaluation (e.g., calculation of allele and genotype frequencies,

determination of Hardy-Weinberg equilibrium). Of note, literature evaluation skills should include the ability to assess the validity and significance of gene-drug response associations. Furthermore, students should be taught the theory and limitations of regression analyses, multiple comparisons, and other complex analyses that are often used to identify genes of interest and evaluate their impact on drug response.

Several resources available through the World Wide Web offer valuable information about genetic variants linked to disease risk, phenotype, and drug response. The National Institutes of Health supports the following genomic and pharmacogenomic resources:

- Pharmacogenomics Knowledge Base (PharmGKB; <http://www.pharmgkb.org>)
- Database of Genotypes and Phenotypes (dbGaP; <http://www.ncbi.nlm.nih.gov/gap>)
- Single Nucleotide Polymorphism database (dbSNP; <http://www.ncbi.nlm.nih.gov/SNP/>)

Other valuable resources include the Web site of the International Serious Adverse Event Consortium and the Health and Human Services Web site on Personalized Health Care Initiative. It is essential that pharmacy graduates be familiar with how to locate, navigate, and use Web sites, such as those previously listed, as resources of genomic information.

Benchmark Performance Measures

- Pharmacy graduates will be able to predict the effects of DNA sequence variation and epigenetic mechanisms on human physiology, pharmacokinetics, and pharmacodynamics.
- Pharmacy graduates will be proficient in the retrieval of genomic information from primary literature, genomic databases, and other resources to assist with drug therapy decisions.

- Pharmacy graduates will be able to appropriately assess the strengths, limitations, and clinical significance of genetic association studies.
- Pharmacy graduates will be able to apply concepts of genetic variability to individualize patient care plans and achieve optimal pharmacotherapeutic outcomes.

Biotechnology

- Curricular Outcome #8: Describe the basic utility and limitations of commonly used genetic assays.
- Curricular Outcome #9: Develop a basic understanding of interpretation of pharmacogenomic test results.

Discussion

The level of understanding in the utility and limitations of genetic assays should be comparable with that of other clinical assays introduced in the pharmacy curricula, such as international normalized ratio (INR) and lipoprotein assays. An understanding of the basic technology for describing and evaluating genetic material, including polymerase chain reaction and DNA sequencing, is important for a solid foundation in pharmacogenomics. Key focus areas include recognition of the available and promising methodologies to assess genetic material; general knowledge of the handling and manipulation of genetic materials within assay protocols; and comprehension of the components measured with key assays.

With the increased availability of genetic technology, including tests marketed directly to the consumer, patients may gain access to their genetic information with minimal counseling support. Pharmacists may assist patients with questions regarding test results, but theoretical comprehension of the science and technology alone will not provide a professional service to

patients. Therefore, it is recommended that pharmacists develop the skills necessary to interpret the following genetic information: genetic laboratory test results, assay accuracy and reliability, and limitations of methods and analyses.

As genetic medicine evolves, the pharmacy curricula will need to be flexible to adapt to the changing technology. In the future, scientists may find it necessary to sort through large amounts of genomic data to identify relevant information for pharmacotherapeutic decision-making. Although pharmacists will likely not be directly involved in interpreting complex genetic data, graduates should possess sufficient knowledge to allow effective communication with biostatisticians, bioinformatics specialists, and other genetic experts and be an integral part of an interdisciplinary group to optimize pharmacotherapy. This comprehension will be similar to the counseling competencies currently required for drugs and other pharmaceutical products, such as interpreting the INR in relation to warfarin therapy. Thus, pharmacy graduates, in collaboration with essential personnel, should be able to effectively interpret and apply laboratory findings to drug therapy.

Suggested Implementation

Whether obtained in the pharmacy curriculum or through prerequisite requirements, formal education in the classroom and/or laboratory is recommended. Student exposure should include access to current and accurate information provided by active genetic researchers in person or through alternative media formats. Pharmacy students should undergo training for interpreting pharmacogenetic testing results. The expertise of genetic researchers, biostatisticians, and others will be necessary to ensure that appropriate information is transferred.

Benchmark Performance Measures

- Pharmacy graduates will be able to describe basic genotyping technology and its application to patient care.
- Pharmacy graduates will be able to effectively communicate with scientific experts and other clinicians for interpreting and addressing genetic test results with respect to pharmacotherapy.
- Pharmacy graduates will be able to effectively communicate with patients to explain pharmacogenetic test results and recognize when patient referral to an expert in genetics is necessary.

Bioinformatics

- Curricular Outcome #10: Show proficiency in the evaluation of genetic data and information.

Discussion

As genetic information is incorporated into therapeutic decision-making, the ability to manage and decipher large quantities of information will become increasingly valuable for health care professionals. Many genes and genetic variants likely influence the response to most drugs. The ability to implement genetically guided therapeutic interventions will therefore require that data on several genes and gene variants be obtained, processed, analyzed, and interpreted appropriately and efficiently. This will likely require interdisciplinary efforts by scientists and clinicians.

Computational applications will be essential to decipher the large amount of data for a given patient that may be generated from sequencing and gene expression studies.

Bioinformatics is the use of computer programs or mathematic models to obtain useful information from “noisy” data that are caused by high-throughput assays, such as DNA sequencing and microarrays. The pharmacist will likely not need to be an expert in mathematic and statistical methodology in relation to pharmacogenomics. However, pharmacists should be familiar with genetic-based software programs, as they become available, and be able to assess output from probabilistic or other relevant models. The depth of knowledge required may not be different from the early implementation of therapeutic drug monitoring into clinical practice and the development of pharmacokinetic modeling software that incorporated Bayesian estimators to predict optimal drug doses. The BLAST (Basic Local Alignment Search Tool), which allows comparisons of a query nucleotide or protein sequence with similar database sequences, and Ensembl, which allows the identification of the location and relationships of individual genes, are examples of freely accessible bioinformatics tools that should be familiar to pharmacists.

Ultimately, genetic output will be integrated with clinical variables to predict optimal drug dosing. This is already in progress clinically as testing for variants that alter warfarin dosing, and response is gaining scientific validity and transitioning into clinics. Pharmacy graduates should be prepared to evaluate whether and when to use genetically guided dosing algorithms and, if deemed appropriate, understand how to use such algorithms to determine drug dose.

Suggested Implementation

Pharmacy curricula have adapted to the need for training in health information technology and have incorporated courses in bioinformatics, with clerkships in bioinformatics available at some institutions. The curricula should continue to evolve by including genetic information as it becomes available for clinical use. The suggested implementation is to include a new course or incorporate material into an existing course dedicated to bioinformatics, with more time devoted to genetically guided drug therapy. The application of genetically guided therapy could then be reinforced in a coordinated manner with a clinical pharmacotherapy course using available software programs or algorithms to predict drug response.

Benchmark Performance Measures

- Pharmacy graduates will show the ability to assess the strengths and limitations of the genetic algorithms and probabilistic models used to estimate appropriate drug therapy and/or dose.
- Pharmacy graduates will be able to use genomic-based software within the context of the patient's clinical factors to individualize therapy.

Summary

Ensuring that the pharmacy curriculum addresses issues with respect to advances in genomics is crucial for preparing the pharmacy workforce to perform valuable services in managing personalized, pharmacogenomically driven therapy. Our committee identified four key areas deemed essential components of the pharmacy curriculum:

- personalized medicine concepts and terminology
- genomic applications in basic and applied pharmaceutical sciences

- biotechnology
- bioinformatics

Although there were some differences in opinion among committee members with respect to the depth or extent of material taught in each of these sections, there was unanimous agreement that the curricular outcomes described were the minimum expectations for future pharmacists to provide optimal patient care in the era of personalized medicine. Schools may wish to offer elective courses to provide additional and more in-depth instruction in one or more subjects. Material taught in each area should evolve together with progress in the field. This is particularly true for gene-drug response associations, biotechnology, and bioinformatics. Self-directed learning behavior should be encouraged whenever possible to better prepare students to advance their skills and knowledge of the science. Finally, faculty development will likely be necessary for the widespread education of pharmacy students in personalized medicine. Professional pharmacy organizations can provide a valuable service by providing this education.

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