

2006 marked the 40th year of publication for *The Annals*. Throughout its history, *The Annals* has provided important contributions to the development of clinical pharmacy. In 2007, we are continuing to publish articles reflecting on the history of clinical pharmacy through the eyes of practitioners, including those pioneering clinical pharmacy, as well as those who have more recently entered the profession and a well-established specialty. In addition, we are presenting articles and editorials from the early history of *The Annals* that have given direction and shape to the practice of clinical pharmacy (see page 2042).

Emergence and Evolution of Pharmacogenetics and Pharmacogenomics in Clinical Pharmacy over the Past 40 Years

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Although discoveries relating abnormal chemical or drug responses to heritability were first described more than 100 years ago, the term *pharmacogenetics* was first published in 1959, and it is within the past 40–50 years that pharmacogenetics/pharmacogenomics has emerged as an individual field of study.¹ Pharmacogenetics generally refers to the effects of one or a small number of genes on drug response or pharmacokinetic profile. Often used interchangeably with the term pharmacogenetics, pharmacogenomics denotes a broader, more large-scale study of the effects of genome-wide differences on drug response or pharmacokinetics.

With pharmacogenetics just emerging as a field in the late 1960s, it should not be surprising that neither pharmacy in general nor clinical pharmacy in particular had described a role for the field in practice. While many pharmacists played important roles in pharmacogenetics research around this time, it wasn't until the early 1990s that pharmacogenetics became a topic of discussion in professional pharmacy journals.^{2,3} It was also at this time when there were larger scale discussions about how such advances in biotechnology might impact pharmacy practice and education.⁴

Both pharmacogenetics and clinical pharmacy have grown considerably but largely independently of each other over the past 40 years. The discovery of the debrisoquine hydroxylase (later identified as CYP2D6) polymorphism in the late 1970s emphasized the significant role that single gene mutations could have on response to a wide variety of drugs, building on investigations of primaquine sensitivity and prolonged succinylcholine response, both of which focused on variability impacting relatively few drugs.¹ Around this same time, recognition that most drug responses were determined by multiple genes and various factors governing gene and protein expression and function gave rise to pharmacogenomics, expanding the field beyond the implied single gene focus of pharmacogenetics. Scientific and technological breakthroughs in molecular biology and computer science (eg, polymerase chain reaction, microarrays, bioinformatics) have considerably advanced the genetics and genomics fields. Linked with these innovations is arguably the greatest scientific accomplishment of this time period: initiation and completion of the Human Genome Project.^{5,6} This project is critical to the continued growth of the field, as it has provided maps that are used as the basis for studies seeking to identify genes associated with specific drug responses or disease risks.

Coincident with the technology advances of the past 40 years, efforts to link scientific pharmacogenetics discoveries and clinical practice have also progressed. While there have been several important accomplishments in this area,

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such as increasingly widespread thiopurine methyltransferase (TPMT) testing to guide azathioprine and 6-mercaptopurine dosing (secondary to known association between low-activity TPMT variants and the risk for hematologic toxicity from standard thiopurine doses), formation of the Pharmacogenomics Research Network (PGRN) and efforts by the Food and Drug Administration (FDA) to begin considering pharmacogenomics data stand out as particularly important. The PGRN is funded by the National Institutes of Health and serves to connect researchers interested in pharmacogenomics to facilitate studies of the genetic determinants of drug response.⁷ In addition to the individual scientific discoveries by the members of this network since its creation in the late 1990s, the PGRN can also be credited with building and maintaining the leading pharmacogenomics database in the field (PharmGKB; www.PharmGKB.org), which on its own is an invaluable asset for furthering scientific and clinical advancement in the field. While the PGRN and PharmGKB help in the discovery of clinically important pharmacogenomics data, the FDA's issuance of a draft guidance on pharmacogenomics signals official recognition of the high likelihood that pharmacogenomics will continue to be an increasingly important consideration for drug therapy and that such pharmacogenomic factors should be formally considered in the drug approval and surveillance processes.⁸ Although still in a nonbinding draft guidance form, these guidelines call for the submission of pharmacogenomic data from industry sponsors and are intended to facilitate the use and collection of pharmacogenomic data during drug development.

While clinical pharmacy as a whole has grown and evolved over the past several decades, the specialty of pharmacogenomics clinical pharmacy is still in its infancy. Broader changes in recent years, however, have had an impact and are likely to continue having an impact on the development of clinical pharmacy in the pharmacogenomics field. One important change has been the shift toward more of a clinical focus in pharmacy education at the expense of basic science education. The philosophy that "pharmacy students and graduates of professional degree programs in pharmacy are not scientists and should not be expected to be scientists" but instead should "use science ... in their practice to solve problems," as stated by an academic affairs committee of the American Association of Colleges of Pharmacy (AACP) is of obvious importance to considerations of how the profession will embrace a field whose foundations, applications, and advancements are so intertwined with basic science.⁹ Similarly, while the shift to having the PharmD the only recognized entry-level degree may be perfectly in line with the profession's move to have a greater clinical role, many have argued that this shift has come at the expense of both basic science education and

pharmaceutical sciences programs.^{10,11} In recognition of the potential importance of pharmacogenomics in guiding drug therapy decisions, there have been some important moves by the profession to directly address this still-emerging field. The first was the establishment by the National Coalition for Health Professional Education in Genetics (of which AACP, the American College of Clinical Pharmacy, and the American Society of Health-System Pharmacists are member organizations) of a set of core competencies in genetics that all health professionals should possess.¹² The second was the charge made by AACP to its 2001–2002 academic affairs committee to consider how pharmacogenomics might impact pharmacy education and to make recommendations regarding how to appropriately train students in this area.¹³ Both of these may seem small steps, but they represent an official commitment to the idea of a minimum set of standards for genomics knowledge and at least the beginning of addressing what needs to be done to allow us to meet these standards.

The era of clinical pharmacogenomics has arrived. Although it has not made the grand entrance to the clinical arena that many expected, the ability to use pharmacogenomic data to guide therapeutic decisions is now upon us. Dozens of drugs, including irinotecan, thioridazine, mercaptopurine, and imatinib, among many others, now include pharmacogenomic data in the product labeling.¹⁴ While not quite yet considered the universal standard of care, drug selection and/or dosing based on the results of a genomic test has become common for multiple drugs at many institutions, and recently, the FDA approved the first clinical test for mutations in the CYP2D6 and CYP2C19 enzymes, making such broadly applicable pharmacogenomic data available to virtually all prescribers.

Today, pharmacy lies at an interesting point with respect to pharmacogenomics (and similar fields, such as proteomics, which refers to the comprehensive study of the structure and function of all of the body's proteins) in that the profession seems yet to have committed to any particular direction. Individual pharmacist–researchers are actively involved in cutting-edge pharmacogenomics research, with some even leading some of the individual research groups within the PGRN. Many clinical pharmacists are aware of genetic sources of variable drug response and may even consider such factors regularly in their practice. Curricula at colleges and schools of pharmacy and topics addressed at professional meetings are changing to reflect the emergence of pharmacogenomics.^{15–17} However, despite all of these changes, there seems to be both disagreement about the adequacy of the current depth/breadth of pharmacy education^{10,18–22} and uncertainty regarding what role pharmacy will have or should have as pharmacogenomics becomes more widely applicable in clinical practice.¹⁸

Given our focus on drugs, high degree of visibility, and easy access for patients, pharmacists seem particularly well suited to take the lead role in incorporating and using pharmacogenomic data in clinical practice. Some have even likened the use of pharmacogenomic data in practice to therapeutic drug monitoring, a role that pharmacists have certainly claimed in most practice settings.²³ Although there is considerable debate about whether pharmacists are interested in or capable of serving in this role,¹⁸ it is a role that some healthcare professionals will need to fill if pharmacogenomics even comes close to the prominent role many have claimed it will have. To this end, continued development of a pharmacogenomics specialty within clinical pharmacy is a worthy short-term goal for the profession to help fill the current void in the area and to help the profession transition into the future. For the long-term future, however, it is likely that all pharmacists, regardless of practice site, will need to be able to understand and apply pharmacogenomics in practice. Despite the considerable uncertainty that exists regarding the future of clinical pharmacogenomics, there are some aspects of its future with respect to clinical pharmacy that are a bit more certain:

1. Pharmacogenomics will continue to have a significant impact on research and will continue to become increasingly relevant to patient care. These trends will continue regardless of what the pharmacy profession does concerning pharmacogenomics in education or practice.

2. Without a clear and concerted effort to improve pharmacists' knowledge not only of pharmacogenomics but also of the basic and biomedical sciences supporting the field, the pharmacy profession will not be in a position to convincingly claim any specific role with respect to utilizing pharmacogenomics in practice. While there have been positive initiatives in the area of pharmacogenomics education at both the student and postgraduate levels, recent surveys have shown that pharmacists' knowledge in these areas is relatively poor and that less than half of schools and colleges of pharmacy provide any structured pharmacogenomics instruction; even those that do allocate surprisingly little time to it, given the complex nature of the entire topic (eg, science/technology aspects, clinical trial/drug development aspects, clinical application, cost-effectiveness issues, legal and ethical concerns).^{15-17,24}

3. Business considerations will play a significant role in the movement of pharmacogenomic testing and labeling into the clinical arena, a move that will likely take place before most health professionals and systems are adequately prepared to use such data. Two examples of this include the availability of pharmacogenomic data in the package labeling of numerous drugs (without readily available testing methods) and the approval and marketing of a commercial pharmacogenomic test for certain drug-metabolizing enzymes (despite uncertainty about how to use the resulting information).

4. Pharmacy is not the only medical specialty dealing with the question of how to best prepare itself for the changes that will accompany more widespread clinical application of pharmacogenomics. Medicine, too, even with an arguably greater basic science emphasis, has discovered that most new graduates and practicing physicians do not have a sufficient pharmacogenomics background.²⁵ This is presented not to diminish the urgency with which pharmacy should act to better educate its members, but rather to emphasize the need that exists for a genomics-educated drug expert as a part of the patient care team.

Several things need to happen for pharmacy to be able to identify its own role in a future where genomics are a major consideration in drug selection, dosing, and monitoring. First, pharmacy needs to identify what exactly its role should be. Do we seek to continue in a role as advisors on drug therapy or should our future include a more direct role in drug selection, dosing, and monitoring? It is likely that pharmacogenomics will increase the complexity of patient care and increase the reliance on teams of healthcare professionals to provide care.²⁶ Consequently, pharmacy needs to define its future role in this context, working with pharmacists in various practice settings and with professionals from other disciplines. As discussed previously, given pharmacists' education and training, pharmacy should claim responsibility for any aspect of care involving drug therapy. Second, coincident with claiming a greater responsibility for patient care, pharmacy must be willing to accept the responsibility and liability that will come with any new or expanded role. It has been predicted that incorporation of pharmacogenomics into practice will increase the liability associated with both drug prescribing and dispensing²⁶ because of the perception that such individualized therapy will greatly minimize treatment failures and adverse reactions. If pharmacy wants its role to include aspects of drug/dose recommendations, prescribing, and/or monitoring/follow-up, then pharmacists must embrace the associated responsibility that will come with that role. Third, pharmacy must work to diligently document the outcomes of any such pharmacogenomics-related drug selection/dosing efforts, just as it has with therapeutic drug monitoring and other clinical pharmacy-related recommendations. This will validate our value in any new patient care role and contribution to the healthcare team. Considering that such documentation is a part of many pharmacists' practice today, it should not be an extremely difficult step, but with our arguments for greater patient care responsibility, such documentation will be even more important than it is today. Finally, a reevaluation and evolution of pharmacy education is necessary. As discussed in detail previously, pharmacogenomics is a field soundly based in basic and biomedical sciences, and for pharmacists to be adequately prepared to apply genomics data in practice, a concerted effort to teach both pharmacogenomics and its

associated science and clinical topics is critical. We cannot even begin to make our case for an expanded role in patient care without being able to show that we can bring a level of expertise (eg, pharmacogenetic and other factors influencing drug selection and dosing) that is not already provided by other members of the healthcare team.

It remains to be seen exactly what impact pharmacogenomics will have on clinical practice, but genomics data are already being used to tailor drug selection and dosing decisions in specific situations. Certainly, genomic information is not widely used today, and there are many obstacles that must be overcome before more personalized drug therapy becomes the norm. However, there is no longer a question of whether or not pharmacogenomics will be important; pharmacogenomics-based drug therapy will continue to be more and more common in clinical practice. While pharmacists have played a significant role in advancing pharmacogenomics research, the specialty of pharmacogenomics clinical pharmacy is still in its infancy. The continued development of this specialty and the incorporation of pharmacogenomics into all pharmacists' knowledge base depend on the profession's willingness to make some difficult changes. With adequate preparation, the broader incorporation of pharmacogenomics into clinical practice should bring with it greater opportunity for pharmacists to use their expertise regarding drug therapy and a greater chance to positively impact patient care.

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