Integrating Pharmacogenomics into Pharmacy Practice via Medication Therapy Management

A whitepaper developed by the American Pharmacists Association.

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American Pharmacists Association

Abstract

Objective: To explore the application and integration of pharmacogenomics in pharmacy clinical practice via medication therapy management (MTM) to improve patient care.

Data sources: Department of Health & Human Services (HHS) Personalized Health Care Initiative, Food and Drug Administration (FDA) pharmacogenomics activity, and findings from the Utilizing E-Prescribing Technologies to Integrate Pharmacogenomics into Prescribing and Dispensing Practices Stakeholder Workshop, convened by the American Pharmacists Association (APhA) on March 5, 2009. Participants at the Stakeholder Workshop included diverse representatives from pharmacy, medicine, pathology, health information technology (HIT), standards, science, academia, government, and others with a key interest in the clinical application of pharmacogenomics.

Summary: In 2006, HHS initiated the Personalized Health Care Initiative with the goal of building the foundation for the delivery of gene-based care, which may prove to be more effective for large patient subpopulations. In the years since the initiative was launched, drug manufacturers and FDA have begun to incorporate pharmacogenomic data and applications of this information into the drug development, labeling, and approval processes. New applications and processes for using this emerging pharmacogenomics data are needed to effectively integrate this information into clinical practice. Building from the findings of a stakeholder workshop convened by APhA and the advancement of the pharmacist's collaborative role in patient care through MTM, emerging roles for pharmacists using pharmacogenomic information to improve patient care are taking hold. Realizing the potential role of the pharmacist in pharmacogenomics through MTM will require connectivity of pharmacists into the electronic health record infrastructure to permit the exchange of pertinent health information among all members of a patient's health care team. Addressing current barriers, concerns, and system limitations and developing an effective infrastructure will be necessary for pharmacogenomics to achieve its true potential.

Conclusion: To achieve integration of pharmacogenomics into clinical practice via MTM, the pharmacy profession must define a process for the application of pharmacogenomic data into pharmacy clinical practice that is aligned with MTM service delivery, develop a viable business model for these practices, and encourage and direct the development of HIT solutions that support the pharmacist's role in this emerging field.

Keywords: Pharmacogenomics, pharmacy practice, medication therapy management, health information technology, personalized health care.

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Personalized Health Care Initiative

In 2006, then Department of Health & Human Services (HHS) Secretary Michael O. Leavitt saw an opportunity to advance a new kind of medical care: personalized health care (PHC). He defined PHC as "the combination of basic scientific breakthroughs of the human genome with computer-age ability to exchange and manage data."[1] The knowledge created through the completion of the human genome is enabling researchers to characterize variations in the biology of individual patients. Gene-based medicine will help create more effective treatments for large patient subpopulations and is currently being used in practice to treat individual patients.

The PHC Initiative within HHS drew together 50 existing federally supported programs to build the foundation for the delivery of PHC. These activities involve many agencies within HHS, including the National Institutes of Health, Food and Drug Administration (FDA), Centers for Disease Control and Prevention (CDC), Office of the National Coordinator for Health Information Technology, American Health Information Community, the Agency for Healthcare Research and Quality, and Centers for Medicare & Medicaid Services (CMS). Aware that the PHC approach would require a new way of thinking, Leavitt convened a working group (i.e., the Personalized Healthcare Workgroup) to make recommendations in several key areas: information technology, scientific foundations, regulatory guidance, and translation to clinical practice.

This systems approach to health care delivery is in the process of creating tools for electronic transmission of health records and information; conducting innovative research to delve more deeply into the effect of genes on disease progression; establishing a regulatory environment that supports effective development of drugs, diagnostics, and other means to reach specific patient subpopulations; and translating genetic information to clinical practice.

One of the first priorities of the PHC Initiative was establishing a network of electronic health records (EHRs) to ensure the availability of complete patient health information. Individual EHRs give health care providers Health Insurance Portability and Accountability Act–compliant access to genetic testing data when applicable and family health histories to enable health care providers to make more effective treatment and medication decisions. Because EHRs include diagnosis, treatment decisions, and outcomes data for large populations, the information contained in these EHR networks could be potentially used to extend our understanding of best clinical practices, treatment effectiveness, variations in patient response to therapy, and safety issues and potentially through the FDA's evolving Sentinel Initiative, a national electronic system designed to improve FDA's ability to track the safety of drugs.[2]

Other health information technology (HIT) efforts include creating secure EHRs that protect patient privacy and standards for metabolic data used in drug research and clinical decision making. A number of efforts focus on integrating genetic data into clinical practice. This requires developing new software packages that incorporate genetic data to help with clinical decisions. As the tests evolve and the results become less variable, decision support tools also should evolve to reflect added consistency.

Another priority area for the PHC Initiative was to improve scientific understanding of the interplay between genetics, disease, lifestyle, and environment. Understanding the genetic and molecular disposition of diseases and chronic conditions also gives health care providers and patients tools to predict which patients may manifest a particular disease or condition. This information will allow patients and health care providers to take steps to prevent the onset of disease. If tests reveal certain disease biomarkers (i.e., chemical or molecular activity correspond-

At a Glance

Synopsis: Findings from the Department of Health & Human Services Personalized Health Care Initiative, Food and Drug Administration (FDA) pharmacogenomics activity, and the American Pharmacists Association–convened Utilizing E-Prescribing Technologies to Integrate Pharmacogenomics into Prescribing and Dispensing Practices Stakeholder Workshop were evaluated to determine how pharmacogenomics could be integrated into pharmacy clinical practice via medication therapy management (MTM), with the goal of improving patient care. Drug manufacturers and FDA have begun to incorporate pharmacogenomic data and applications of this information into the drug development, labeling, and approval processes. New applications and processes for using this emerging pharmacogenomics data are needed to effectively integrate this information into clinical practice. To achieve this integration, pharmacy must define a process for the application of pharmacogenomic data into pharmacy clinical practice, develop a viable business model for these practices that encourages and promotes the use of the clinical expertise of pharmacists, and encourage and direct the development of technology solutions that support the pharmacist's role in this emerging field.

Analysis: *As the models of integration and application of pharmacogenomic data continue to evolve, pharmacists must further develop a process to effectively deliver pharmacogenomic services to individual patients that is aligned with MTM service delivery. Realizing the potential role of the pharmacist in pharmacogenomics through MTM, however, will require connectivity of pharmacists into the electronic health record infrastructure to permit the exchange of pertinent health information among all members of a patient's health care team. Although pharmacogenomics has tremendous potential to affect patient care with the current system, addressing current barriers, concerns, system limitations, and developing an infrastructure by which all health care providers can work collaboratively and collectively to effectively gather, store, and apply pharmacogenomic data will be critical to improving patient care, achieving better outcomes, and enhancing health care delivery.*

ing to a disease), then treatments can be started before the disease becomes entrenched. Finally, an individual's genetic and personal health history provide a starting point for treatment decisions involving drug therapy. A patient's genetic blueprint can provide a roadmap to determining the drugs that will offer the most effective response. This has the potential to improve patient safety and outcomes.

As PHC evolves and is integrated into practice, patients are benefiting from the application of genetic information. One of the earliest diagnostic tests developed gauges a patient's drug metabolism. The results of a simple assay can show if a patient has a specific combination of genetic variations in two liver enzymes that alone metabolize nearly 45% of all drugs. Depending on the outcome, physicians can tailor dosages based on molecular metabolism rather than weight.

In cancer treatment, genetic testing can pinpoint patients who will benefit from certain drug therapies. For a woman with breast cancer, a diagnostic test can determine her tumor's genetic signature. If the patient tests positive for human epidermal growth factor receptor 2 (HER-2), she can be given trastuzumab, which suppresses excess HER-2 and cuts the risk of disease recurrence by 50%.

The regulatory component of the PHC Initiative supports development of drugs, diagnostic tests, and medical products focused on specific patient subpopulations. Keeping pace with the rapid rate of scientific and medical advances is challenging to agencies charged with oversight. FDA's Critical Path Initiative—a national strategy for transforming the way FDA-regulated medical products are developed, evaluated, and manufactured—for example, has identified 76 scientific and regulatory areas in which progress is needed to improve and expand the science base for medical product development. FDA also is working to evaluate in vitro diagnostic tests that will reveal predisposition to diseases. Bioinformatics is another important field in realizing PHC. Computer models can assist in predicting drug effectiveness and safety and arrive at those predictions using genetic factors.

A number of challenges must be overcome to fully realize the promise of PHC. First, biomedical research and HIT research must continue to move forward. This requires continued funding of innovative ideas. Translating these ideas into practical activities must be a priority. Second, user-friendly clinical decision support and information management tools are needed to drive evidence-based care into clinical settings. In addition, the relations among government, industry, and academia will continue to evolve as these groups work together to expand discovery opportunities, improve safety, and lower financial risks when developing molecular therapies and diagnostics. Finally, PHC must be delivered in a sound financial way. Preventing or treating disease early provides an intrinsic cost savings. Molecular information allows for more effective, tailored treatments that could reduce costs substantially by eliminating expensive, ineffective individual therapies.

Because PHC requires integration of many components, former HHS Secretary Leavitt anticipated the time to implement the PHC paradigm would likely take a generation. What began as a federal program will transform into a collaborative effort engaging both private industry and academia. Physicians, pharmacists, other health professionals, and patients will work together with the architects of the PHC framework to realize the full potential of PHC (Figure 1).

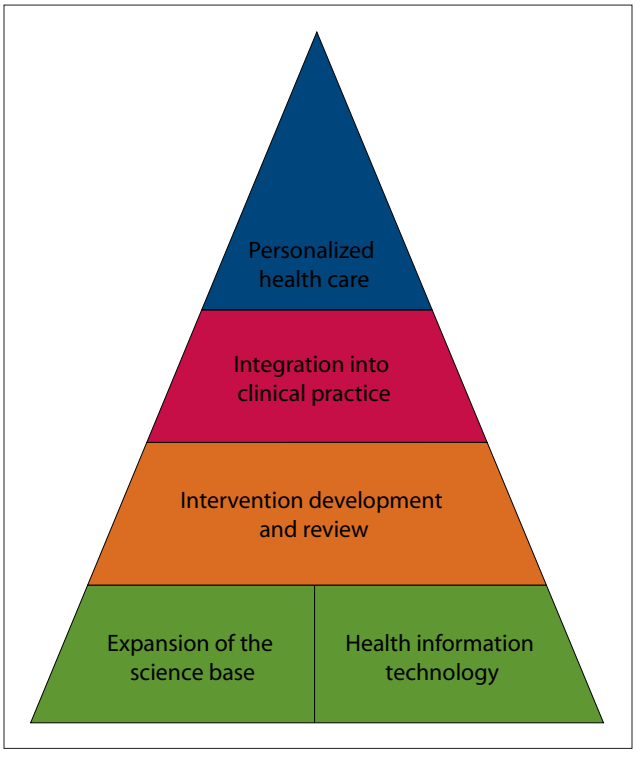

Figure 1. Personalized health care building blocks

Source: Department of Health & Human Services. Personalized health care: opportunities, pathways, resources. Washington, DC: Department of Health & Human Services; 2007:9.

Pharmacogenomics and FDA

Drug manufacturers and FDA have already started incorporating pharmacogenomics into the drug development, labeling, and approval processes. Effectively transmitting genomic information to and from health care providers is challenging because of lack of awareness, privacy concerns, and the lack of a robust, nationwide electronic health care infrastructure. As progress is made in each of these areas, the potential of pharmacogenomics will be incorporated into improved patient-centered care processes resulting from the development of proactive safety tools that will be integrated into the health care system.

Recognizing the valuable role that genomics data can play in evaluating drug safety and effectiveness, FDA initiated the a voluntary data exchange program (i.e., "safe harbor" agreement) in 2003. This program asked companies to submit voluntarily genomic data along with their drug submission packages. More drug companies are now including genomic and other biomarker information in their new drug applications.[3] These more comprehensive drug applications offer the potential for more targeted patient therapies. However, FDA Commissioner Margaret Hamburg acknowledged in 2009 that "genomics represents a chal-

lenge as well as a unique opportunity" for the agency.[3] To take advantage of genomics data, FDA participates in the HHS PHC Initiative, which is aimed at creating a foundation to use pharmacogenomic data in drug development and clinical practice. Through a number of working groups, the program also establishes a framework for electronic transmission of pharmacogenomic data from current EHR databases.

FDA also is reexamining how it shares information among divisions and with other federal agencies. In 2009, Hamburg noted that "incorporating genomics into medical product review requires an interagency, multi-disciplinary effort that transcends the boundaries of an existing center."[3] Intra- and interagency collaboration in the areas of research, oversight, and enforcement will be a key mode of operation to managing genomic data successfully. In addition, regulatory bodies must seek input from industry and other stakeholders to discover barriers that may stall innovation and forward progress.

Because personalized medicine requires close alignment of diagnostics and drugs, FDA currently is evaluating how it reviews drugs and diagnostics. In 2004, the agency found itself scrambling when presented with a microarray device to identify variations in cytochrome P450 (CYP)2D6 and CYP2C19, which are enzymes that play a major role in drug metabolism. At the time, FDA had few scientists on staff with sufficient knowledge to fully evaluate the product. Getting up to speed on the product and its intended use took time. The agency is developing new guidance for industry in personalized medicine. One guidance document will describe the criteria FDA will use to evaluate disease biomarkers. The second guidance document will clarify the agency's expectations for the kinds of clinical trials and levels of confidence needed to demonstrate that a diagnostic test is accurate and can be used for clinical assessments.[4]

Because pharmacogenomic data can help clinicians tailor drug therapies to specific subpopulations of patients, the information should be readily accessible. Although hard copy package inserts that include pharmacogenomic information are useful, a more robust health information infrastructure that includes pharmacogenomic dose responses and other details would enable health care providers to make real-time and potentially lifesaving decisions when prescribing medications.

For instance, breakthroughs in understanding the relationship between genetics and drug metabolism have caused FDA to issue changes to drug labels, most recently in the case of a number of approved drugs. In the case of clopidogrel, new findings demonstrating that patients with genetic variants of CYP2C19 may not effectively convert the drug to its active form caused FDA to issue a new label warning in March 2010.[5] Similar actions based on new genetic findings have been taken for warfarin and morphine.[6,7] In the case of cancer drugs such as cetuximab, new findings suggested testing patients for *K-RAS* mutations before starting therapy because those individuals may not benefit from the drug. This information was added to the drug label in July 2009.[8] Changes in drug labeling are likely to continue as more retrospective studies are conducted on approved drugs and new studies are performed on emerging therapeutics.

Pharmacogenomics: Pharmacist's role in personalizing medication therapy

As the 21st century moves into its second decade, pharmacogenomics (i.e., the use of genetic information to predict an individual's response to a drug) will play an increasing role in drug development and clinical treatment decisions. Using patients' genetic information to tailor drug therapy will reduce the risk of adverse events, potentially improve patient outcomes through targeted therapies and dosing, and create a more efficient, cost-effective drug development process. By transforming a one-size-fits-all approach to drug therapy into a patient subpopulation or patient-specific approach, the pharmaceutical and clinical communities are one step closer to achieving the new medical paradigm of personalized health care.

Pharmacists can serve an integral role in applying pharmacogenomics into clinical practice to improve the quality and safety of health care. As pharmacogenomic applications continue to advance, the pharmacy profession has begun to define its role and address steps to effectively integrate this emerging field into clinical practice. One avenue to implementing the PHC Initiative is by integrating it into clinical pharmacy practice through medication therapy management (MTM). This service optimizes therapeutic outcomes for individual patients.[9] As key health care providers in MTM service delivery, pharmacists assess and evaluate a patient's complete medication therapy regimen via a comprehensive or targeted medication therapy review, rather than focusing on a specific therapy product.[10] By gathering key pieces of information (e.g., all medications a patient is taking, including supplements), pharmacists can assess potential interactions, recommend alternative therapies to reduce medication-related adverse effects, and effectively collaborate with the individual patient's other health care providers to improve overall care and treatment outcomes.

In diverse patient care settings, pharmacists currently are providing MTM services to help patients achieve improved treatment outcomes. Pharmacist-provided MTM provides unique new and emerging opportunities to integrate pharmacogenomics into clinical practice and actively engage in collecting, interpreting, and using pharmacogenomic data to improve patient care. As stated by former HHS Secretary Leavitt, "Pharmacists have always been on the front line in guiding consumers about the appropriate use of their medical products. With the advent of pharmacogenomics and increasingly individualized care, pharmacists will continue to have an important role in improving the quality and safety of patient care."[11]

At the patient–physician level, a new model is needed to advise on pharmacogenomic results because most genetic counselors are not equipped to fully assess the genetic contributions to the overall pharmacological treatment of medical conditions. Incorporating pharmacogenomics into MTM service delivery allows pharmacists to lend their expertise to the treatment planning process to optimize treatment outcomes. Because of their in-depth training specific to medications, pharmacists, working collaboratively with the prescriber and the lab, could review all of the medications prescribed for a patient and the patient's genomic data and offer an assessment on whether a prospective drug would provide the best fit for the condition and patient. As part of a collaborative health

care team, pharmacists can optimize drug choice and dosage and, if needed, suggest alternatives to maximize therapy outcomes.

Although using pharmacogenomic information has many benefits, determining how to disseminate those data to health care providers remains a challenge. Currently available e-prescribing systems offer one venue of dissemination. However, e-prescribing platforms are generally being integrated into EHR functionality, and the integration and movement of pharmacogenomic information within the EHR as a component may offer a more viable option for the exchange of this information. To develop a pharmacogenomic component within EHR, groups that are creating pharmacogenomic data and those who will use the data must identify key pharmacogenomic elements that will be most effective in clinical treatment decisions. Although the challenge is complex, work has begun in a number of areas to bring the promise of pharmacogenomics to patients. Moving forward, the pharmacy profession must define a process for the application of pharmacogenomic data into pharmacy clinical practice that is aligned with MTM service delivery, develop a viable business model for these practices that encourages and promotes the use of the clinical expertise of pharmacists working in collaboration with other health care providers and labs, and encourage and direct the development of technology solutions that support the pharmacist's role in this emerging field.

Pharmacists and HIT

The pharmacy profession has been a leader in the health care industry in electronic connectivity, establishing standards for real-time claims adjudication and other processes dating back several decades. This history combined with its strong foundation in e-prescribing platforms and evolving EHR infrastructures has positioned pharmacy for establishing a model for incorporating pharmacogenomics into EHR. Although e-prescribing offers one option for storing, transmitting, and sharing pharmacogenomic data, considerable work remains in developing and harmonizing standards to integrate the information into clinical and pharmacy records, transmitting the data between users, and creating interoperability among organizational systems. In the long run, connecting EHR through emerging health information exchanges and among various health care providers, including pharmacists, may be a more efficient and effective method for the movement of pharmacogenomic data than using e-prescribing.

In the 2006 report Preventing Medication Errors, the Institute of Medicine recommended that all prescriptions be written and received electronically by 2010.[12] Although this goal was challenging, the pharmacy community was well equipped to move toward it. The profession has taken the lead in developing electronic formats to transmit and receive prescriptions. In 2001, the National Association of Chain Drug Stores and the National Community Pharmacists Association founded Surescripts, an e-prescribing network. By the middle of the decade, more than 90% of U.S. community pharmacies were connected and could receive prescriptions electronically.[13]

According to Surescripts, by the end of 2010, nearly 235,000 prescribers were using e-prescribing and the number of prescriptions routed electronically had grown from 191 million in 2009 to 326 million in 2010.[12]

Federal EHR programs

The federal government has a number of programs to spur the adoption of e-prescribing tools and electronic health records through the American Recovery and Reinvestment Act of 2009 (PL 111-5).[14] Additional federal money is available to prescribers adopting e-prescribing tools through the Medicare Improvements for Patients and Providers Act of 2008 (PL 110-275).[15] Although current e-prescribing infrastructure may facilitate the sharing of pharmacogenomic data in the short term, viable long-term integration into pharmacy clinical practice will only be achieved if pharmacy management systems become recognized as EHR or EHR modules, contain certified common functionalities and data elements, and are incorporated within the broader EHR infrastructure.

Stakeholder efforts

In fall 2010, the Pharmacy e-Health Information Technology Collaborative was formed by nine national nonprofit pharmacy organizations. Since that time, the Collaborative has increased in size by the addition of several key industry stakeholders as associate members. The Collaborative's goal is to ensure that the pharmacist's role of providing patient care services, including MTM, is integrated into the national HIT interoperable framework. The Collaborative is pursuing EHR standards for pharmacists and pharmacy providers that effectively support the delivery, documentation, and billing of pharmacist-provided patient care services across all patient care settings. Efforts are under way currently to promote the adoption of the recently balloted and approved functional profile for pharmacist/pharmacy provider EHR that will facilitate the movement of relevant patient-specific information, including pharmacogenomic data, to a patient's entire health care team, including pharmacists, through a practice site's information management system.[16] Connectivity for pharmacists to the EHR infrastructure will be critical as pharmacists continue to expand their role as patient care providers and increase their involvement in the application of pharmacogenomics to improve patient care and outcomes.

Personalized health care delivery

Pharmacists will play a leading role as the health care system moves toward the paradigm of personalized health care. Through MTM initiatives, pharmacists have already been repositioning themselves as integral players in a coordinated health care approach to patients—one that emphasizes collaboration among health care providers, patients, and insurers. MTM is a comprehensive patient care service that provides valuable treatment information to all of the patient's health care providers. MTM focuses on the entire spectrum of medication used by a single patient. This approach gives patients a coordinated approach to therapies that may not be achieved using more traditional methods. Developing standardized processes for incorporating pharmacogenomic drug data in the MTM care process will contribute to improved decision making on the proper selection and use of medications and contribute to the achievement of the best outcomes for individual patients.

Implications for the health care system

Integrating pharmacogenomic data into clinical practice will likely increase patient safety and reduce costs. It's estimated that 1.5 million preventable serious medication errors occur annually in the United States.[17] Those numbers translate into $177 billion spent on services associated with the corresponding illness and death. In addition, nearly 40% of the compounds in the drug pipeline are targeted therapies. A majority of these drugs will be prescribed for oncology applications and will take into account a patient's genetic or biomarker information.[18]

Genetic information may come from clinical trials, personal testing, and drug development. Careful collection, compilation, storage, dissemination, and protection of the information is critical. Such a system will produce an effective and efficient tool for researchers, industry, and the clinical community to use in the therapy decision-making process and will have a considerable effect on the health care system. Regulatory, clinical, and scientific personnel are collaborating to develop a knowledge base of drug therapy and pharmacogenomics that will inform decisions as information technology personnel build electronic patient management systems.

Pharmacogenomics has tremendous potential to affect patient care within the health care system positively. Addressing current barriers, concerns, and system limitations and developing an infrastructure for the future in which all health care providers can work collaboratively to improve the care of patients through the application of pharmacogenomic data in clinical practice will undoubtedly improve patient care, achieve better outcomes, and enhance health care delivery.

Exploring pharmacy's role in pharmacogenomics: A 2009 APhA Stakeholder workshop

To explore developments in pharmacogenomics and the role it can play in clinical pharmacy practice, APhA gathered leaders at the request of HHS from pharmacy, medicine, and HIT at an APhA Stakeholder Workshop titled Utilizing E-Prescribing Technologies to Integrate Pharmacogenomics into Prescribing and Dispensing Practices, held on March 5, 2009. The stakeholder workshop provided an overview of personalized medicine and pharmacogenomics within HHS; an update on the state of HIT, EHRs, and e-prescribing; an overview of pharmacogenomics from theory to practice; and defined steps for moving forward.

Overview

The invitational meeting offered a venue for the pharmacy profession to discuss the current state of pharmacogenomics, past successes, future challenges, and the profession's pathway forward for integrating pharmacogenomics into clinical pharmacy practice. At the outset of the meeting, participants heard the following challenges for integration: (1) genetic tests exist for only a small number of drugs and diseases, (2) clinicians and insurers want evidence that genetic tests add value to prescribing decisions, (3) a lack of familiarity with genetic information diminishes its impact on treatment decisions, and (4) a limited information infrastructure fails to provide access to an ever-expanding reservoir of genetic information to treat patients. Participants discussed how new HIT strategies might improve the flow of pharmacogenomic information between providers and pharmacists, discussed the challenges associated with integrating pharmacogenomic data with EHRs, and made recommendations to overcome those barriers.

Key stakeholder workshop presentations, discussions, and comments

An overview of personalized medicine and pharmacogenomics within the Department of Health & Human Services and the Food and Drug Administration: The science of testing

Presentations by: Gregory Downing, DO, PhD, Project Director, Personalized Health Care Initiative, Department of Health & Human Services; and Issam Zineh, PharmD, Associate Director for Genomics, Center for Drug Evaluation and Research, Food and Drug Administration

Downing. Downing discussed how advances in both genetic research and HIT have provided a foundation for pharmacogenomics. The HHS PHC Initiative was launched to expand and harness the power of these enabling technologies to improve health care safety, quality, and effectiveness. Downing described the following PHC goals:

- Continued development and expansion of the biomedical science base to address genetic aspects of disease and prevention
- Creation of a secure electronic national health information system that can store, assemble, exchange, and analyze genetic data and serve both researchers and clinicians
- Partnerships with industry to translate robust genetic and clinical research into innovative medical products and services that are safe and effective
- Integration of genetic knowledge, decision tools, and therapeutic approaches into widely used clinical practice

Downing emphasized that pharmacogenomics represents the leading edge of genomics in health care. He warned that simplistic characterization of personalized medicine would lead to unfulfilled expectations. He also suggested that opportunities exist for mass customization of technologies and tools.

Zineh. Zineh stated that FDA has "reached a critical mass of interest in personalized therapeutics." Personalized medicine first became a priority for FDA in 2002, and since that time, the agency has been building the scientific and regulatory infrastructure needed to support the emerging field. Zineh described the voluntary genomic data submission process in which drug developers, academic researchers, and others share genetic data or other biomarker data of a particular drug with FDA for scientific exchange purposes. These data may include those on variable drug response or adverse events. This information is provided under a "safe harbor" agreement mechanism that allows for the exchange of data without regulatory consequences.

According to Zineh, FDA is taking greater initiative and asking new drug sponsors to look for genetic biomarkers that might be associated with drug response or adverse effects. Since 2004, FDA has received approximately 50 voluntary and exploratory data submissions spanning all major therapeutic areas. Over time, as genetic biomarkers are discovered and validated, Zineh predicted that a larger proportion of new drug approvals will be labeled with genetic indications or dosing recommendations. The number of investigational new drugs applications for which the Center for Drug Evaluation and Research Services Group has been consulted has nearly quadrupled since 2008. Similar growth has been seen with new drug applications and biologic license applications. Zineh suggested that many more drugs may require genetic testing to establish dosing regimens.

FDA affirms that pharmacogenomics may be the key to improving the safety and efficacy profile of many drugs already on the market, as currently available pharmacogenomic tests help predict patients who are likely to respond to drugs and those who may suffer serious adverse effects or fail to

respond. Zineh stated that signals that a drug may be a candidate for pharmacogenomic review may come from many sources, including a drug sponsor, academic researchers, and reports in MedWatch or FDA's own literature reviews. For example, FDA's collaboration with Medco is expected to help assess the pharmacogenomic safety and efficacy of many currently marketed drugs. In deciding whether to recommend or require pharmacogenomic testing on a drug label, Zineh said the agency considers the severity of potential drug-related adverse events and whether they are likely to be rare or certain for specific genotypes.

Currently, clinicians do not commonly order and insurers do not regularly pay for pharmacogenetic testing, even when genetic biomarker information is on a drug label, according to Zineh. Physicians and payers want evidence that using genetic testing in treatment decisions produces a better outcome than conventional prescribing practices. However, that assessment presupposes a body of clinical evidence on which to base such comparisons.

Determining the level of evidence needed to recommend genetic testing is an area of debate. FDA urges the health care community to consider a "realistic" level of evidence in the area of pharmacogenomics. Zineh urged that this emerging field not be held to higher standards of evidence than other health care services. He also referred to a published report finding that only 15% of clinical practice guidelines are based on rigorous clinical evidence; the rest are based on expert opinion.

In closing, Zineh asked participants to consider how HIT could help advance the practice of "precision medicine."

Discussion. In the discussion following Zineh's talk, a majority of participants expressed surprise at the number of drugs in the pipeline that are likely to have pharmacogenomic information in the label. Participants discussed the standard of evidence that should accompany specific pharmacogenomic applications into the clinic. Many observed the need to move away from randomized controlled trials (RCT), noting that although RCTs are the gold standard to examine questions of efficacy, good epidemiologic study designs based on existing data could be important in identifying genetic risk factors for drug safety. As an example, the decision to relabel carbamazepene for genetic risk of Stevens-Johnson syndrome was based on evidence from 60 or 70 people who suffered the reaction and shared a similar genetic ancestry. Participants agreed that relabeling drugs based on genetic data would be greatly accelerated if researchers could query large clinical data sets that include both genetic and drug history information.

Participants also noted that the availability and likely proliferation of genetic tests to predict drug safety and efficacy adds another layer to prescribing decisions and amplifies the need for better tools and structures to support clinical decision making. The challenge, participants agreed, is to develop information structures that streamline and improve the decision-making process. Orderly introduction of pharmacogenomics into the clinical setting will require knowledge and information technology to converge.

Others suggested that convincing demonstration projects would be helpful, and all agreed that education and payment policies aligned to support pharmacogenomics will be needed. Downing noted that CMS is beginning to move in this direction and is exploring issues surrounding clinical use of genetic tests in order to develop policies that will guide coverage decisions.

Summary. Genetics research will drive new approaches to diagnostics and treatment focused on key patient subpopulations rather than a one-size-fits-all approach. To ensure access to and continued development of genetics-based research and related technologies, HHS launched the PHC Initiative. FDA is developing a regulatory framework to process genetic drug data, which industry is willing to supply. Determining the level of evidence needed for clinical applications of pharmacogenomic data is a matter of debate. The challenge is to develop structures to streamline and improve the decision-making process for both drug approval and clinical application.

Update on the state of health information technology, electronic health records, and e-prescribing: Transitioning pharmacogenomics to e-prescribing and electronic health records

Presentations by: Ken Whittemore Jr., BSPharm, MBA, Senior Vice President of Clinical Practice Integration, Surescripts; Lynne Gilberston, Vice President of Standards Development, National Council of Prescription Drug Programs; and David Collins, Director of Healthcare Information Systems, Health Information and Management Systems Society

Beginning in 2004, the U.S. government began a focused effort on developing a nationwide EHR platform. An executive order by then President George W. Bush created the position of National Health Information Technology Coordinator, and the White House urged access to EHRs for all Americans by 2014. The final numbers for a 2008 National Center for Health Statistics study showed that 21% of all U.S. office-based physicians used an EHR system. Preliminary results for the 2009 study showed a jump to 27%.[19]

As a result of stimulus funding from the American Recovery and Reinvestment Act of 2009, $2 billion in grants and loans were provided to the Office of the National Coordinator for Health Information Technology to encourage adoption of HIT. An additional $17.2 billion has been set aside for Medicare and Medicaid to reward hospitals and physicians for using electronic systems.

Whittemore. Whittemore described e-prescribing as the complete, bidirectional, electronic transmission of prescription information. He estimated that e-prescribing saves pharmacies $1.07 per new prescription and $.42 per refill. Of greater importance is the role e-prescribing can play in delivering better care to patients. For example, e-prescribing network systems can consolidate prescription histories from multiple pharmacies, both community and mail service, into one patient record to make potential interactions more obvious.

Whittemore also noted that physician participation in e-prescribing system networks has grown exponentially, in part because of Medicaid and Medicare incentives. Roughly two-thirds of e-prescriptions handled by Surescript, an e-prescribing network, are generated by EHR systems, and even small practices without EHRs are using freestanding e-prescribing systems to provide this functionality.

He noted that although pharmacogenomic information can be transmitted in e-prescriptions, work is needed to develop and harmonize standards to integrate information into clinical and pharmacy records. A dialogue between the pharmacy community and information technology developers would allow development of data elements and format for pharmacogenomic information and determine how those data will be used. Will it be given as information only, as part of the continuity of care record (i.e., a standardized format for the electronic exchange of health information), or as part of an automated drug use review process? After the standards are in place, technology vendors must incorporate them into their products, but this will occur only if they see a demand from physicians and pharmacists for pharmacogenomic data as an integral part of prescribing and dispensing medication.

Gilbertson. Current e-prescribing system standards continue to evolve. The industry standard for electronic exchange of information between physicians and pharmacists is SCRIPT. Gilbertson said that the standard, which is maintained by the National Council for Prescription Drug Programs

(NCPDP), includes prescription and refill information, sections on drug history, medication alerts, drug allergies, and compound ingredients. NCPDP is working on enhancing SCRIPT to enable physicians and pharmacists to exchange clinical information about a patient through follow-up questions and answers. New features also will automate prior authorization, predetermination of benefits, and patient financial responsibility when the medication is dispensed.

Meeting participants noted that including clinical information in the e-prescribing platform provides a foundation for integrating pharmacogenomic data into clinical and pharmacy practice. A pharmacogenomic profile could show the patient's drug metabolizer status or trigger medication alerts that could reduce the risk of adverse reactions. Components such as automated preauthorization also will improve workflow for the pharmacy system. As more pharmacogenomic data are provided for individual drugs, the need for prior authorization before dispensing the drug is likely to increase. An e-prescribing component that obtains information directly from a physician or patient's EHR regarding whether a genetic test has been performed and the test results would reduce costs and administrative burden on the pharmacy system considerably.

Collins. To achieve an integrated HIT system, Collins suggested that pharmacy providers, clinicians, HIT professionals, and vendors define how pharmacogenomic information will be represented and stored in both clinical and pharmacy records and what level of interoperability will meet clinical and administrative needs. He said that by statute, EHRs must include not only patient demographic and clinical health information but also clinical decision support, physician order entry, and the ability to exchange electronic health information with other sources. By integrating these features with pharmacogenomic data into national EHR standards from the outset, a more robust system will be achieved. All of these actions must occur in a timely fashion because the deadline for a national EHR system is 2014, with gradual phase-in of adoption over the next several years.

Discussion. Following Collins's presentation, participants discussed whether the larger hurdle is integrating EHRs into health care or integrating pharmacogenomics into EHRs. Some standalone e-prescribing systems have no means of integrating and sharing laboratory test results and cannot support pharmacogenomics. In some cases, users of large EHR systems urge their vendors to create specific applications or they do it themselves.

Harnessing the power of the growing body of pharmacogenomic data will remain difficult until the data are standardized into a form that is easily retrievable and analyzed. Creating a powerful decision-making tool for clinical practice requires a strong health care information infrastructure. At a national level, much emphasis has been placed on developing an EHR platform that would include a patient's demographic and clinical health information, as well as clinical decision support, physician order entry, and the sharing of information throughout the health care community. In their current form, EHR systems cannot provide the analysis and functionality needed to incorporate pharmacogenomics into treatment decisions.

Summary. E-prescribing is becoming a common tool in the health care community. Standards harmonization remains a challenging area, and ongoing work is needed to ensure e-prescribing systems that fit the needs of physicians and pharmacists. The pharmacy and information technology communities must continue to collaborate to develop EHR and e-prescribing platforms. E-prescribing platforms provide a key foundation for integrating pharmacogenomics data into clinical pharmacy practice. Pharmacogenomic components should be built into EHR systems from the outset.

Pharmacogenomics from theory to practice: Integrating pharmacogenomics into clinical practice

Presentations by J. Russell Teagarden, BSPharm, MA, Vice President of Clinical Practices & Therapeutics, Medco Health Solutions; Mary W. Roederer, PharmD, CPP, Research Assistant Professor, Eshelman School of Pharmacy, University of North Carolina; Grace Kuo, PharmD, MPH, Program Director, Pharmacogenomics Education Program, Skaggs School of Pharmacy, University of California, San Diego; and Kevin Donnelly, Vice President, SNOMED Terminology Solutions, College of American Pathologists

Roederer. Knowing how to interpret pharmacogenomic data will become central to prescribing situations in the near future for physicians and clinical pharmacists, according to Roederer. Although only a handful of drugs now include notices about genetic testing prior to prescribing the drug (Table 1), new notices are likely to appear on many more drugs in the future. This is a result of heightened awareness of the impact of genetics on drug metabolism. Roederer noted that hematology and oncology are two areas leading the way in which genetic information is used to guide therapy. As discussed above, warfarin and clopidogrel are two of the most well-known examples in hematology.

Table 1. FDA requires, recommends, or provides information on genotyping for the following drugs and biomarkers

Warfarin (CYP2C9; *VKOR*)
Trastuzumab (Herceptin; *HER2-neu*)
Imatinib mesylate (Gleevec; C-kit mutations, *BCR/ABL* translocation)
Maraviroc (*HIV-CCR5* receptor site)
Celecoxib (CYP2C9)
Cetuximab (EGF receptor)
Azathioprine and mercaptopurine (TPMT deficiency)
Irinotecan (*UGT1A1*; homozygous for the *28 allele)
Carbamazapine (*HLA-B*5101*)
Gefitinib (EGF receptor mutations)
CYP2D6 and CYP2C19

Abbreviations used: CYP, cytochrome P450; EGF, epidermal growth factor; FDA, Food and Drug Administration; TPMT, thiopurine methyltransferase.
Source: Mary Roederer, Eshelman School of Pharmacy, University of North Carolina, Chapel Hill.

Roederer discussed that although pharmacogenomics is slowly beginning to show its promise in clinical situations, it faces several hurdles. These include (1) actually ordering a pharmacogenomic test, (2) obtaining test results quickly, (3) ensuring that the results are accurate, (4) determining the level of evidence required to support the results, and (5) obtaining reimbursement for the test.

The actual use of pharmacogenomic data is spotty at best across specialties. For example, Roederer noted that in oncology, the medical community generally has not recommended that RCTs show the usefulness of genetic testing. However, when evidence is available for the tests in trials and the evidence has shown that they can affect treatment outcomes, the medical community has used the information in clinical practice. The case for genetic

testing and use in treatment decisions is unclear in the case of tamoxifen, which is a commonly prescribed drug shown to assist in limiting breast cancer recurrence. Studies have shown that patients who are low metabolizers do not experience the same positive effects from the drug as those who are high metabolizers. In 2006, an advisory committee recommended adding genetic testing information to the label; however, because the committee could not agree on whether testing should be recommended, FDA did not change the label.[20]

Another challenge to implementing pharmacogenomics in clinical settings is obtaining genetic information quickly. In the case of warfarin, to guide dosing, a laboratory must be able to provide genetic data on drug metabolism within 24 hours. A report in Seizure suggested that POLG DNA sequencing should be performed before administering valproic acid for pediatric seizures disorders, in order to reduce the odds of liver failure.[21] If this become a standard of care, clinicians will need a fast turnaround on the DNA sequencing test.

From the perspective of her clinical practice and experience in the application of pharmacogenomic data, Roederer explained that the small number of genetic tests currently available and validated by FDA makes ensuring results a challenge. Most of the tests currently used are provided by the laboratories that developed them and most of these tests are not formally reviewed by FDA. After the test results are available, interpreting them is a lengthy process that requires knowledge of the test itself, the interplay of the genetic variants and the drug, and the patient's clinical situation.

Increasing education about pharmacogenomic testing and the clinical applications is critical because in the area of oncology drugs, for example, therapies are effective in only about 25% of the population receiving them. Arthritis drugs have a 50% effectiveness rate and asthma drugs about a 60% effectiveness rate.[22]

Teagarden. Several factors will drive the standardization and integration of clinical pharmacogenomic data within EHRs and e-prescribing systems, according to Teagarden. The first is a greater emphasis on pharmacovigilance. Access to genomic data allows providers/payers to analyze trends in adverse drug reactions and flag potential connections to genetic mutations. In addition, he noted, genetic information readily available in patient records hastens identification of potential gene–drug interactions. A second factor to drive incorporation of pharmacogenomic information into health records is a growing interest among patients in learning their genetic background and having it available to health care providers. Finally, as clinical decisions rely more on genetic information, electronic support systems will have to store, analyze, and adapt to new and evolving genetic data. As genetic testing becomes more routine—as part of well visits and patient history—it should be incorporated into the patient's EHR.

Teagarden stated that a collaboration between Medco and the Mayo Clinic has shown that genetic testing and follow-up counseling to patients helped avoid adverse reactions and save money, according to Teagarden. As part of the initiative, which involved 105 payers and 6 million covered lives, Medco offered genetic testing through its partner LabCorp to any patient who submitted an initial claim for either warfarin or tamoxifen. If test results showed a mismatch between the patient and the drug or prescribed dose, the patient's physician was notified.

Kuo. The medical community is at a disadvantage when it comes to knowledge about genetic research and development because of its relative newness and the volume of research available. Kuo discussed that programs at medical and pharmacy schools across the country are needed to provide education resources on pharmacogenomic theories and clinical applications. Kuo noted that many observers believe that the key rate-limiting step in clinical integration of pharmacogenomics is the cursory exposure to medical genetics that most health professionals receive during their training.

Kuo described a pilot program (PharmGenEd) that was developed at the Skaggs School of Pharmacy, University of California, San Diego. PharmGenEd provides a suite of tools, including continuing medical education courses, Internet-based lectures, curricular modules for pharmacists, and presentations at professional meetings. Through these learning aids, the developers are seeking to familiarize health professionals with the challenges and opportunities that genetic tests offer to clinical treatment situations. The program aims to demystify pharmacogenomics. PharmGenEd is attempting to reach 100,000 pharmacists, physicians, student pharmacists and medical students, and other health professionals. The program is supported by CDC and works closely with national pharmacist and medical associations.

Donnelly. One aspect of a pharmacogenomic information component could be an electronic tool that would organize and relate all the systems within the human body to all of the drugs that can influence those systems, Donnelly noted. Such a tool would assist clinicians in making use of increasingly complex pharmacogenomic data in clinical situations. Building in a matrix-of-interactions tool would deliver much needed support in making individual treatment decisions.

As developers plan EHR systems, they must build in flexibility so that the system can adapt to include new information resulting from research advancement. If evidence is available to support changes in drug labeling through the application of pharmacogenomic information, this information should be included in the EHR system and supported by clinical decision support tools so that clinicians can review the information and use it in conjunction with FDA labeling recommendations.

Summary. One of the key challenges to integrating pharmacogenomics into practice is educating the entire spectrum of health care providers about pharmacogenomics, the technologies of pharmacogenomics, and how to develop and apply the technologies. Despite the promise of pharmacogenomics, few practitioners use genetic data in treatment decisions. The limited availability of validated genetic diagnostics that rapidly return results makes obtaining data difficult. Two factors that will drive demand for testing are pharmacovigilance and patient demand for genetic data. Better education and decision support tools will help the health care community embrace pharmacogenomics in clinical settings.

Defined steps for moving pharmacogenomics in clinical practice forward

Workshop participants agreed that pharmacists and physicians must deliver a unified plan to HIT developers and vendors that underscores the need for clinical record and e-prescribing systems to incorporate pharmacogenomic information and related decision support tools. Achieving these goals will require clinicians and pharmacists to work with standard-setting bodies. The pharmacy and medical communities will need to make a cogent case for the benefits of pharmacogenomics because HIT developers and standards organizations must balance a myriad of requests for the EHR system.

In addition to education, participants at the stakeholder workshop identified the following action items for potential users of electronically transmitted pharmacogenomic data.

Practitioners should:

- Identify what pharmacogenomic data are needed to make relevant clinical decisions, who should have access to the information, and what level of detail should be shared among providers.
- Resolve issues related to who (physician or pharmacist) will handle interpreting and applying genetic test data to medication management.
- Work with HIT vendors on standardized transmission of genetic and pharmacogenomic data.
- Convey the need for secure electronic transmission of genetic/pharmacogenomic data to HIT vendors.

Facilities should:
- Use broadband to enable better information exchange among health care workers and patients.
- Update software/hardware to support data exchange.
- Adopt guidelines, policies, and procedures related to privacy, confidentiality, and ethics.
- Consider policies that align system gains with individual practitioner efforts.
- Integrate pharmacy point-of-care genetic testing, ensuring that data are readily retrievable and easily shared.

Patients/consumers should:
- Obtain a baseline level of understanding of pharmacogenomics.
- Engage in an informed understanding of privacy/security risks and protections.
- Appreciate the benefits of pharmacogenomics.
- Discover mechanisms for patients to order valid tests directly from labs.

Payers should:
- Run return-on-investment analysis, including credible third-party cost-effectiveness analysis for pharmacogenomic tests/drugs.
- Identify "low-hanging fruit" in pharmacogenomics applications that can improve patient outcomes and save money.
- Align financial/reimbursement incentives/disincentives for adoption.
- Offer team/outcome-based payment reform rather than a "silo-based" provider payment model.
- Remove payers from the clinical decision process.

Regulators/standards development organizations should:
- Develop point-of-care testing guidelines/protocols/standards.
- Request pharmacist input and access to EHR standards development.
- Conduct demonstration projects.
- Expand labeling to require pharmacogenomics information where available (include data in Investigational New Drug applications).
- Harmonize standards, terminologies, and their uses.
- Not regulate the clinical use of pharmacogenomics;
- Facilitate professional organizations to develop appropriate guidelines and requirements.

Vendors should:
- Deliver integration, interoperability, and seamless incorporation into practices/facility workflow.
- Build decision tools for prescribers.
- Comply with HITSP (Health Information Technology Standards Panel) and other relevant standards and participate fully in the interoperability development process.
- Publish industry guidelines for "floor" requirements of professional tools.

Education organizations should:
- Encourage innovative practice models that use genomic information in clinical decision making.
- Disseminate lessons learned, barriers, and successes.
- Integrate pharmacogenomics into clinical and didactic education throughout curricula (e.g., PharmD, MD, DO, RN).
- Include interprofessional training and practice models at the degree, residency, and fellowship levels.
- Integrate pharmacogenomics into community-based public health programs.

Research and development should:
- Create better clinical diagnostic support tools.
- Use clinical outcome and pharmacogenomic information for rare disease discovery and research and development on new drug targets.
- Develop trials to answer the question of what clinicians should do with pharmacogenomic information (e.g., avoid a particular drug, increase/decrease dose).
- Assist industry in determining exactly what to build first: what do we want?
- Increase funding for health systems research, including education methods and population health monitoring.
- Develop a matrix to capture genomic information relevant to each drug and related to drug–drug interactions for all pertinent classes of drugs.

APhA2010 House of Delegates adopted policy

To further promote the importance of pharmacogenomics in personalized medicine, the APhA House of Delegates adopted the following policy at its March 2010 meeting in Washington, DC.

Pharmacogenomics/personalized medicine

1. APhA supports evidence-based personalized medicine, defined as the use of a person's clinical, genetic, genomic, and environmental information to select a medication or its dose, to choose a therapy, or to recommend preventive measures, as a means to improve patient safety and optimize health outcomes.
2. APhA promotes pharmacists as health care providers in the collection, use, interpretation, and application of pharmacogenomic data to optimize health outcomes.
3. APhA supports the development and implementation of programs, tools, and clinical guidelines that facilitate the translation and application of pharmacogenomic data into clinical practice.
4. APhA supports the inclusion of pharmacogenomic analysis in the drug development/approval and postmarketing surveillance processes.

Conclusion

All drugs are not created equal, neither are the patients who use them. Shifting the health care paradigm from one that is reactive to one that is proactive, preemptive, and personalized will take money, research, and collaboration. Transforming the current enterprise to a patient-focused, participatory endeavor will benefit patients, providers, and payers. As with all beginnings, the final path remains undecided but the goal is clear. Personalized health care can reach patients through improved understanding of the interaction between genetics and drug metabolism. After these connections are made, regulatory bodies such as FDA must act on the information and convey it to health care providers. Pharmacists providing MTM, working in collaboration with physicians, can tailor drug therapies to patient subpopulations and individuals through the effective application of pharmacogenomic data. Pharmacists have the potential to become integral players in the personalized health care paradigm. Their keen awareness of drug–drug interactions and drug metabolism make pharmacists indispensible resources when considering treatment choices. If a patient with a genetic variant is at risk for adverse drug effects, the pharmacist can suggest dosage adjustments, alternative drugs, or anticipate and manage potential adverse effects.

To achieve the integration of pharmacogenomics into clinical practice via MTM, the pharmacy profession must define a process for the application of pharmacogenomic data into pharmacy clinical practice that is aligned with MTM service delivery, develop a viable business model for these practices that encourages and promotes the use of the clinical expertise of pharmacists, and encourage and direct the development of technology solutions that support the pharmacist's role in this emerging field. To maximize the pharmacist's contributions to pharmacogenomic applications, continued work by the profession in these key areas is important.

Through the electronic interchange of pharmacogenomic data across an EHR that is harmonized and interoperable among all health care providers, including pharmacists, the application of pharmacogenomic data into clinical practice will improve efficiency, reduce costs, and, most importantly, achieve a more personalized treatment approach and better outcomes for each patient.

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