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Academic Centers Play a Vital Role in the Study of Drug Safety and Effectiveness

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Prescription drugs have enormous potential to improve health and longevity, and the past decades have witnessed remarkable innovations in the pharmaceutical marketplace. Despite this, the past decades are also replete with examples of therapies, ranging from thalidomide to rofecoxib to sibutramine, that have raised important safety concerns. The recent outbreak of fungal meningitis linked to unsterile practices at a compounding pharmacy serves as yet another cautionary tale that all drugs have risks and that drugs are manufactured, produced, delivered, and administered in a complex regulatory and clinical environment. In response to challenges threatening the safety of prescription drugs; regulatory agencies, pharmaceutical firms, and academic institutions monitor and evaluate pharmaceutical risks and benefits, all the while advancing the science of pharmacoepidemiology. However, unlike other fields of epidemiology, the regulatory and clinical contexts within which drugs are developed, manufactured, prescribed, dispensed, and used provide distinctiveness to the discipline of pharmacoepidemiology.

Unlike regulatory agencies and the pharmaceutical industry, academia has unusual independence and autonomy in the generation of fundamental new knowledge to advance scientific understanding and public health. Thus, investigators at academic institutions have a particularly valuable role to play in this developing field. We describe some opportunities and challenges in ensuring that the US population has access to safe and effective medications and explain the unique contributions of academia to the study of drug utilization, safety, and effectiveness.

The Food and Drug Administration (FDA) has long been charged with the evaluation of the safety of drugs after market approval. Despite this, during the past decades, the Agency has undergone significant structural changes that have advanced its ability to fulfill this mandate. Midway through the past decade, a series of highly publicized concerns regarding the safety of drugs culminated in a pivotal report by the Institute of Medicine that focused on postmarketing surveillance.¹ This report revealed serious resource constraints that were weakening the quality of drug safety monitoring and recommended organizational change in

the FDA as well as implementation of intramural and extramural programs to strengthen risk identification and assessment.

Soon after this report was published, passage of the FDA Amendments Act of 2007 increased the FDA's regulatory authority over postmarket surveillance.² For example, the FDA Amendments Act gave the Agency greater authority to require manufacturers to conduct postmarket risk assessments and to implement risk management programs to monitor and ensure safer use of their products. The Act also apportioned to the FDA the resources needed to develop epidemiologic and informatics capabilities for its drug safety initiatives, such as authorization for access to disparate data sources to establish a postmarket risk identification and analysis system.³

As a result of these changes, the FDA, in coordination with the Office of the National Coordinator for Health Information Technology, launched the Sentinel Initiative to create a national, integrated electronic system for monitoring medical product safety in 2008.⁴ The pilot program of this system, Mini-Sentinel, has leveraged a distributed data network that captures information from administrative data and electronic medical records routinely collected by medical practices, hospitals, health plans, and insurers.^{5,6} To date, the Mini-Sentinel system, which includes administrative and claims data for >300 million person-years, has executed several hundred programs in response to FDA queries.⁷

During the past decade, a convergence of factors, including the costs of emerging health technologies and the increased demand for health care, has also prompted efforts to enhance the value of prescription drugs, devices, and other technologies through comparative effectiveness research.⁸ Such research may be used by many different stakeholders. Clinicians may weigh the effectiveness of new drugs against existing therapies during routine clinical care. Insurance companies can use information on the comparative clinical effectiveness and cost-effectiveness of drugs and other medical products to structure formularies and payment policies. Professional organizations can use comparative effectiveness research results to develop clinical guidelines for their members. As the largest payer of prescription drug costs through Medicare and Medicaid, the US government has an especially important stake in finding and implementing the best evidence on the comparative effectiveness of therapeutics.⁹

The Medicare Prescription Drug, Improvement, and Modernization Act of 2003 authorized the Agency for Healthcare Research and Quality (AHRQ) to fund research about the effectiveness and appropriateness of health services, including prescription drugs.¹⁰ Despite formidable and well-described barriers to implementation that account for the "knowledge gap,"¹¹ the evidence from this research has also been used by public and private health plans to inform coverage decisions, by professional and patient care organizations to create practice guidelines, and by other organizations for performance measurement. Comparative effectiveness research further expanded with the American Recovery and Reinvestment Act (ARRA) of 2009, which appropriated \$1.1 billion to provide patients, clinicians, and others with evidence-based information to make informed decisions about health care.¹² A variety of projects were funded with ARRA monies, leading to the development of longitudinal claims databases, distributed data networks, patient registries, and data infrastructure

valuable for studying drug effectiveness and safety. The Patient Protection and Affordable Care Act of 2010 included provisions for patient-centered outcomes research with the goal of generating information helpful for decision making so that patients can attain their preferred outcomes.¹³ This, too, encompasses research to maximize the safe and effective use of medications in practice.

Pharmacoepidemiology is a vital foundation for the initiatives described previously herein: to shore up the drug safety system and to generate and implement information about comparative effectiveness. No rigorous assessment of drug safety or effectiveness can be performed without the routine application of methods from this discipline, which, in turn, draws on the fields of epidemiology, clinical pharmacology, and medicine. Much of the drug safety and effectiveness research uses observational data and requires the application of advanced epidemiologic reasoning and methods to understand causal effects and to address frequent biases that may be present. When head-to-head randomized controlled trials are impractical or unavailable, observational epidemiologic studies, often based on large health care administrative or electronic health databases, become necessary tools for studying drug effectiveness and safety. These longitudinal databases may capture medical service encounters and pharmacy dispensing information for large, heterogeneous patient populations that are representative of clinical practice in usual care or real-world settings. Of course, although administrative data have the advantage of generalizability, they are prone to threats to internal validity, such as underascertainment of outcomes and confounding by indication.⁹ Thus, sound epidemiologic study designs and solid analytical methods are required to make appropriate inferences about a drug exposure and a safety or effectiveness outcome.

The value of pharmacoepidemiology is universally recognized by important stakeholders of the public and private sectors. During the past decade, the FDA has increased investment in epidemiologists to monitor the utilization of medication, to quantify adverse drug effects, and to evaluate the impact of the FDA's regulatory actions using population-based data.¹⁴ Similarly, most pharmaceutical companies have epidemiologists working to understand the natural history of disease, to quantify background mortality and morbidity patterns, and to evaluate drug safety using observational study designs and methods. The increased need for drug safety and effectiveness research calls for a cadre of highly trained pharmacoepidemiologists to develop and apply the necessary analytical tools and methods. There is a clear need for academic programs that can provide training, mentoring, and resources to the next generation of pharmacoepidemiologists.

Academic university-based programs in pharmacoepidemiology have emerged since the 1990s.¹⁵ Many of these programs also support other intellectual areas that are closely linked to pharmacoepidemiology, such as pharmacoeconomics, pharmaceutical policy, and pharmaceutical health services research, which provide complementary evidence for drug safety and effectiveness. In some cases, the boundaries between these disciplines are blurry. For example, rigorous pharmacoepidemiologic methods are often deployed to evaluate changes in pharmaceutical policy, drawing on both of these disciplines' orientation and insights. Academic programs in pharmacoepidemiology take many different forms: formalized government-academic partnerships, university-based degree-granting programs,

training programs that offer certificates or courses in pharmacoepidemiology, and postdoctoral training programs supported by industry. These programs play pivotal roles in drug safety and effectiveness research by promoting education, research, and public service (Table I).

Academic institutions are also committed to maintaining a healthy pipeline of qualified practitioners and leaders in the field of pharmacoepidemiology; training programs, therefore, must ensure that students achieve core competencies in the field. These competencies were described by Jones et al¹⁶ and can be classified as knowledge-based and functional competencies in pharmacoepidemiology, pharmacovigilance, analysis of exposure data, clinical pharmacology, and medical product regulation (Table II). Academia may also have an educational task of training clinicians in nursing, pharmacy, medical, and dental schools. The provision of pharmacoepidemiology training to clinicians should help them better weigh the risks and benefits of drugs they prescribe.¹⁷

In addition to its roles in education and workforce development, academia contributes to novel approaches to research and capacity building. Several academic programs have established public–private or public–government partnerships that serve as Centers of Excellence for research to support and enhance education and research. For example, the AHRQ’s Centers for Education and Research on Therapeutics consists of 7 academic research institutes that were initiated based on a public–private collaborative model among the federal government, academia, industry, and the public.¹⁸ They have established a core capacity and data infrastructure that enables academic institutions to conduct rigorous scientific research regarding the optimal use of medications, to provide education that will increase awareness of the benefits and risks of therapeutics, and to improve quality while cutting the costs of care.¹⁹ The Developing Evidence to Inform Decisions about Effectiveness network represents a collection of 11 academic research centers funded by the AHRQ to conduct research on the outcomes, effectiveness, safety, and usefulness of medical treatments and services.²⁰ Another example is the ARRA-funded Partnership in Applied Comparative Effectiveness Research, which represents a partnership between Johns Hopkins University and the FDA.²¹ This project is advancing methods for comparative effectiveness research of value to the FDA. The investigators are presently developing tools for projecting the benefits of using adaptive designs, tools for visualizing effects in subgroups, and demonstrations of methods for understanding stakeholder preferences.

In October 2012, we launched the Johns Hopkins Center for Drug Safety and Effectiveness.²² Drawing on the combined expertise in the Johns Hopkins Bloomberg School of Public Health and the Johns Hopkins School of Medicine, the Center is the nexus for individuals at Johns Hopkins who are involved in research, education, clinical programs, and public service to improve prescription drug use and pharmaceutical policy in the United States and around the world. The Center is supporting faculty research and is training a workforce with skills to design and conduct state-of-the-art experimental and observational research in pharmacoepidemiology and drug safety. The Center also has a mission to work with institutional partners to implement processes to ensure safer and more effective use of medicines throughout Johns Hopkins Medicine as well as a public service mission to provide evidence-based information and advocacy about safe and effective medication use

for clinicians, patients, policy makers, and the general public. To focus the work of the Center, we have focused on six core problem areas, ranging from global access and affordability to prescription drug abuse.

Continued implementation of the Affordable Care Act, as well as rapid evolution of electronic health information and redesign of health care delivery systems, will provide new challenges and opportunities for researchers committed to optimizing drug safety and effectiveness. Academic training programs have a vital role to play in this effort, including the production of a workforce with the skills to use the large amount of data generated from integrated electronic health records. These methods will be used to identify early safety signals and to learn the comparative effectiveness of therapies so that clinicians can make optimal choices for their patients. It is an exciting time where there will be major changes in health care delivery in the United States, and pharmacoepidemiologists should have a vital role in this transformation.

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Table I

Expanded roles of academic programs in pharmacoepidemiology.

Education and workforce development
Training and mentoring the next generation of pharmacoepidemiologists
Specialty training of clinicians, regulators, and industry
Research and capacity building
Promotion of partnership with regulatory agencies and industry
Innovation in methods
Development and organization of data repositories
Clinical care and quality improvement
Review of drug utilization and prescription patterns
Surveillance and management of adverse drug events
Implementation of systems to ensure safe and effective medication use in inpatient and outpatient settings
Public service
Dissemination of evidence to patients
Communication to the general public via mass media

Table IIEssential competencies of pharmacoepidemiology. Adapted from content in Jones et al.¹⁶

Category	Items
Knowledge	
Pharmacovigilance	Definitions of adverse event vs adverse drug reaction Meaning/use of spontaneous reports in drug safety
Epidemiology	Basic epidemiology study designs and their usual hierarchy strengths, limitations, and selection of best designs
Prescription data	Types of data on drug use strengths and limitations of cross-sectional prescription data
Functional	
Epidemiology research methods	Design an epidemiology study of both an ad hoc and database type Ensure that the study designs incorporate good pharmacoepidemiology practices Describe methods of statistical analysis and controls for confounding and biases Describe limitations and methods to address these limitations Interpretation of results in the context of public health and regulatory decision making
Professional	
Communications	Communication of results of a pharmacoepidemiology study to a group of nonepidemiology scientists, placing the study and its design in context, explaining strengths and weakness, and options for interpretations and action