

## Cancer Pharmacogenomics and Pharmacoepidemiology: Setting a Research Agenda to Accelerate Translation

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Manuscript received April 5, 2010; revised September 8, 2010; accepted September 10, 2010.

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Recent advances in genomic research have demonstrated a substantial role for genomic factors in predicting response to cancer therapies. Researchers in the fields of cancer pharmacogenomics and pharmacoepidemiology seek to understand why individuals respond differently to drug therapy, in terms of both adverse effects and treatment efficacy. To identify research priorities as well as the resources and infrastructure needed to advance these fields, the National Cancer Institute (NCI) sponsored a workshop titled "Cancer Pharmacogenomics: Setting a Research Agenda to Accelerate Translation" on July 21, 2009, in Bethesda, MD. In this commentary, we summarize and discuss five science-based recommendations and four infrastructure-based recommendations that were identified as a result of discussions held during this workshop. Key recommendations include 1) supporting the routine collection of germline and tumor biospecimens in NCI-sponsored clinical trials and in some observational and population-based studies; 2) incorporating pharmacogenomic markers into clinical trials; 3) addressing the ethical, legal, social, and biospecimen- and data-sharing implications of pharmacogenomic and pharmacoepidemiologic research; and 4) establishing partnerships across NCI, with other federal agencies, and with industry. Together, these recommendations will facilitate the discovery and validation of clinical, sociodemographic, lifestyle, and genomic markers related to cancer treatment response and adverse events, and they will improve both the speed and efficiency by which new pharmacogenomic and pharmacoepidemiologic information is translated into clinical practice.

J Natl Cancer Inst 2010;102:1698–1705

The fields of pharmacogenomics and pharmacoepidemiology are interrelated in that the goal of both is to understand why individuals respond differently to drug therapy, in terms of both adverse effects and treatment efficacy. Pharmacogenomics focuses on understanding how genetic variants that encode for drug-metabolizing enzymes, drug transporters, drug targets, and proteins involved in disease biology influence individual differences in terms of treatment efficacy, effectiveness, and adverse effects. Pharmacoepidemiology uses a variety of study designs to identify patterns and determinants of the use of drug therapy and its effects in clinical and population settings. The study of genomic factors can be readily integrated into pharmacoepidemiologic studies along with nongenetic factors, leading to a natural convergence of the two fields.

Five key trends are creating new opportunities, challenges, and questions in cancer research. These include 1) expanded development and approval of new cancer therapies allowing more therapeutic choices, 2) rapid expansion of knowledge and high-throughput tools to evaluate genomic variation, 3) increasing numbers of cancer survivors who may experience late effects of treatment, 4) widespread use of prescription pharmaceutical agents

in the United States population, and 5) increasing numbers of public-private partnerships and research consortia. The tools and methods of pharmacogenomics and pharmacoepidemiology are well suited to study and take advantage of these trends and to conduct studies that can inform personalized cancer prevention and treatment.

Recent advances in genetic technology, combined with new discoveries in pharmacogenomics, have shed light on the substantial role of genomic factors to predict drug response and the clinical potential of genomic testing. Several pharmacogenomic markers have been or are currently being evaluated to determine their clinical value (Table 1). Examples of these markers include cytochrome P450 2D6 (*CYP2D6*) genotypes in tamoxifen treatment for breast cancer (1), UDP-glucuronosyltransferase 1A1 (*UGT1A1*) genotypes in irinotecan treatment for colorectal cancer (2), and epidermal growth factor receptor (*EGFR*) mutations in non-small cell lung cancer treatment (3,4). These markers may be able to identify subgroups of patients who will optimally benefit from a particular cancer therapy, other patients who might derive little or no benefit, and/or individuals who are at elevated risk for serious

**Table 1.** Pharmacogenomic markers in cancer treatment\*

Biomarkers	Drug	Cancer site	Effect	Information included in the FDA drug label	Routinely used in United States practices
<b>Germline variants</b>					
<i>CYP2D6</i>	Tamoxifen	Breast	Response	No	No
<i>UGT1A1</i>	Irinotecan	Colorectal	Safety	Yes	No
<i>CYP3A4</i>	Dasatinib	ALL	Response	No	No
<i>TPMT</i>	6-MP, 6-TG	ALL and AML	Safety	Yes	Variable
<i>DPYD</i>	5-FU	Breast/colorectal	Safety	No	No
<b>Somatic alterations</b>					
ERBB2	Trastuzumab	Breast	Response	Yes	Yes
KRAS	Cetuximab	Colorectal	Response	Yes	Yes
KRAS	Panitumumab	Colorectal	Response	Yes	Yes
BCR-ABL1	Imatinib	CML	Response	Yes	Variable
KIT	Imatinib	CML/ALL	Response	Yes	Variable
<b>Protein expression</b>					
EGFR	Erlotinib	Lung	Response	No	No
EGFR	Gefitinib	Lung	Response	No	No
Oncotype Dx	Tx Regimen	Breast	Response	No	Yes
Mammoprint	Tx Regimen	Breast	Response	Yes†	No
EGFR	Cetuximab	Colorectal	Response	Yes	No

\* 5-FU = 5-fluorouracil; 6-MP = 6-mercaptopurine; 6-TG = 6-thioguanine; ALL = acute lymphoblastic leukemia; AML = acute myeloid leukemia; CML = chronic myelogenous leukemia; EGFR = epidermal growth factor receptor; FDA = Food and Drug Administration; Tx = treatment.

† Device approval.

adverse events. However, the clinical utility for the most promising pharmacogenomic markers is still being investigated.

A few genetic and genomic tests have recently been integrated into standard clinical practice and/or incorporated into the Food and Drug Administration (FDA) label. However, there appears to be substantial variation in the rate of clinical adoption and acceptance of such testing. At one extreme, testing for *KRAS* mutations to determine whether to use cetuximab and panitumumab in treating metastatic colorectal cancer was adopted quickly (5). By contrast, testing of thiopurine methyltransferase (*TPMT*) genotypes to determine optimal treatment for acute lymphocytic leukemia (6) and of *EGFR* mutations and/or expression to determine non-small cell lung cancer treatment (4) has been variable in clinical practice. So, the discovery of substantial genomic influence over the effectiveness or safety of a cancer drug does not always translate immediately into clinical practice. There may be numerous reasons for this variability: Oncologists may not be convinced that the genomic test is of clinical value, physicians may not know about the tests, drug labels may not describe the usefulness of genetic information, or insurance coverage may not be available for the genetic test (Table 1). For example, in the case of *TPMT* testing, some physicians may not be convinced of its clinical utility and/or cost-effectiveness and they may believe that how they currently manage chemotherapy-induced myelosuppression is an adequate way to screen for potential toxicities. Also, many physicians may have never treated the rare (one in 400) homozygous patient who would experience life-threatening toxicity without *TPMT* testing.

Discoveries from cancer pharmacogenomics and pharmacoepidemiology research can help to optimize the benefit to risk ratio of treatment strategies in general clinical practice. Translation of these discoveries may more efficiently target therapies to patients who will benefit and avoid or anticipate potentially serious adverse events among high-risk patients and thus

may reduce cancer morbidity and mortality and reduce the cost of cancer care. Equally important, these discoveries provide novel insights into the underlying biology of drug response phenotypes. Full realization of the potential of pharmacogenomics research will require the integration of basic discoveries in drug development and pharmacogenomic variability, of genomic and outcome data from phase I–III randomized clinical trials, and of data on the effects of drugs and their interactions with genomic variants in large populations. Here, we report on results from the National Cancer Institute (NCI)–sponsored workshop titled “Cancer Pharmacogenomics: Setting a Research Agenda to Accelerate Translation” which took place on July 21, 2009 and the group’s recommendations to address priorities, resources, and infrastructure needs to advance the fields of cancer pharmacoepidemiology and pharmacogenomic research (7).

## Methods

To address the interdisciplinary and translational nature of this field, and the need for input across various disciplines, the Trans-NCI Pharmacogenomics and Pharmacoepidemiology Working Group (PPWG) was chartered by NCI in January 2008 (8). The PPWG is responsible for planning, developing, directing, coordinating, and evaluating a program of research in pharmacogenomics and pharmacoepidemiology research across NCI. To begin this task, three subcommittees of the PPWG were created to address issues specific to basic biomedical research, clinical research, and population science research. Each subcommittee identified priority areas and research goals important to their specific area of research, analyzed the portfolio of NCI-sponsored pharmacogenomics and pharmacoepidemiology studies of common pharmaceuticals and cancer therapies, and developed recommendations to advance a pharmacogenomics and pharmacoepidemiology

research agenda at NCI. The subcommittee recommendations were then brought to the full PPWG to be combined in a final draft of summary recommendations.

To further refine the recommendations, input was sought from members of the broader cancer research community. In July 2009, NCI brought together these external scientists with representatives of the PPWG, the National Institutes of Health, and other key federal agencies (eg, the United States FDA, the Agency for Healthcare Research and Quality, the Centers for Disease Control and Prevention [CDC], and the Department of Defense) to participate in an NCI-sponsored workshop at which invitees discussed the draft recommendations, priorities for cancer pharmacogenomics and pharmacoepidemiology research initiatives, and the needs of the fields in general. The resulting nine recommendations are presented in this commentary.

## Overview of Recommendations: Future Research Directions

The recommendations reflect the input of NCI and extramural clinical and research investigators from a wide variety of disciplines, including medical oncology, genomics, clinical and basic pharmacology, epidemiology, statistics, health services, pathology, molecular biology, and bioinformatics, among others. The goal of these recommendations is to improve both the speed and efficiency of discovery and the translation of this rapidly evolving new knowledge into clinical practice. These recommendations will serve as the roadmap for the programs, resources, and

infrastructure needed to maintain a pipeline of such discoveries. Here we summarize the priorities relevant to each of the nine recommendations, which have been divided into five scientific-based recommendations and four infrastructure-based recommendations (Table 2).

### Knowledge Gaps in Pharmacogenomics and Pharmacoepidemiology

Recognizing the need to identify gaps in knowledge and to prioritize research, recommendation 1 calls for the development and ongoing support of an expert panel tasked on an ongoing basis to synthesize evidence, identify knowledge gaps, and develop priorities and specific research questions with the goal of speeding translation of pharmacogenomics and pharmacoepidemiology research findings into clinical practice. This group would synthesize and process pharmacogenomic and pharmacoepidemiologic evidence relevant to cancer from trials and observational studies and would provide guidance as to the additional study data that would be needed to translate new evidence into clinical practice. Several ongoing initiatives could be leveraged for this group, of which three are CDC initiatives—the Evaluation of Genomic Applications in Practice and Prevention initiative (9), the Human Genome Epidemiology Network (10), and the new Genomic Applications in Practice and Prevention Network (11)—and one from the National Institutes of Health’s Pharmacogenetics Research Network, the Pharmacogenetics and Pharmacogenomics Knowledge Base (PharmGKB) (12). Ideally comprised of members from the public as well as private entities, the group would consist

**Table 2.** Key recommendations

1. Develop and support a knowledge synthesis study group/board to identify gaps and prioritize cancer pharmacoepidemiology and pharmacogenomic research.
2. Develop and support opportunities to identify clinical, sociodemographic, lifestyle, and genomic markers related to treatment response and/or adverse events in NCI-sponsored clinical trials.
  - Support pharmacoepidemiology and pharmacogenomic studies using previously collected clinical data and biospecimens from existing and ongoing clinical trials.
  - Develop and support opportunities to routinely collect and store DNA specimens in new and existing NCI-sponsored clinical trials for future pharmacogenomic analyses.
  - Develop and support the incorporation of pharmacogenomic markers and/or epidemiological information into the design of clinical trials.
3. Support observational studies that identify clinical, sociodemographic, lifestyle, and genomic factors of treatment response and adverse events.
  - Use predictive clinical, sociodemographic, lifestyle, and genomic factors associated with treatment response and adverse events discovered in clinical trial analyses to develop and support opportunities to validate findings in large, heterogeneous, observational studies.
  - Develop and support opportunities to identify predictive factors of treatment response and adverse events that cannot be obtained using existing clinical trial and correlative study data.
  - Support observational studies of cancer patients (eg, patient cohorts) with standardized protocols and comprehensive biospecimen collections at multiple time points to identify clinical, sociodemographic, lifestyle, and genomic factors that affect cancer treatment and prevention outcomes.
  - Support observational studies of pharmacoepidemiology of cancer prevention and risk.
4. Support basic pharmacology research on the pharmacodynamics, pharmacokinetics, and targets of cancer drugs, and their relationships with genetic variations that affect drug response because of differential gene expression, protein production, receptor-binding affinity, and enzyme level and activity.
5. Provide support for research on the utility of promising pharmacogenetic applications in general clinical practice.
6. Support health information technology enhancements in existing research networks and data systems to facilitate pharmacoepidemiology and pharmacogenomic studies of observational and clinical trial data.
7. Support research on the ethical, legal, social, and data-sharing implications of collecting biospecimens for pharmacogenomics research in population-based and clinical trial research settings.
8. Support the development of transdisciplinary training programs in cancer pharmacogenomics and pharmacoepidemiology.
9. Support, facilitate, and coordinate a trans-NCI effort to partner with other relevant groups, including other federal agencies and industry to develop initiatives and activities in pharmacogenomic and pharmacoepidemiology cancer research that ensure the integration of basic, clinical, and population sciences.

of scientists, policy makers, and patient advocates. Membership should reflect a broad spectrum of expertise, including oncology, genomics, clinical and basic pharmacology, epidemiology, and clinical medicine.

### **Pharmacogenomics and Pharmacoepidemiology Within Clinical Trials**

Recommendation 2 calls for support of the collection, storage, and analysis of biospecimens from clinical trials. The workshop participants noted that in clinical trials, biospecimens are not routinely collected; therefore, the availability of tumor and DNA samples varies considerably across studies. Even when such samples have been collected and stored, there has been limited use of the existing clinical and biospecimens data for pharmacogenomic and pharmacoepidemiologic research. Workshop participants agreed that studies, including genome-wide association studies (GWAS), that use previously collected clinical data and biospecimens from existing and ongoing clinical trials could provide important data that could be rapidly translated into clinical practice and improve treatment management. To promote the pursuit of such studies, it will be necessary to coordinate access, collection, inventory, and pooling of clinical trial data and specimens across trials and across sponsors. Mechanisms for long-term follow-up of clinical trial patients also need to be developed to examine long-term benefits and adverse late effects of various treatments. Last, it is important to develop rapid, open, transparent, and equitable processes for the review of applications for access to these biospecimens.

As of June 2008, more than 300 000 blood samples that had been collected from patients from NCI-sponsored Clinical Trials Cooperative Group Program trials (13,14) were stored in tissue banks. Even more samples are potentially available through the NCI-sponsored Specialized Programs of Research Excellence (15), Cancer Centers (16), and individual investigator research projects. Pharmaceutical company-sponsored studies are another major source of biospecimens if data sharing, material transfer agreements, and access for outside investigators can be negotiated. Important research findings using retrospective analyses of tumor markers from completed clinical trials already have been successfully translated into clinical practice. For example, numerous clinical trials have shown that colorectal cancer therapy with cetuximab or panitumumab is ineffective in tumors with somatic mutations in codons 12 and 13 of exon 2 of the *KRAS* gene. These findings prompted the American Society of Clinical Oncology to develop guidelines to target the clinical use of these drugs based on these genetic markers (17) and the European Medicines Agency and the FDA to include these data in the prescribing information for cetuximab and panitumumab.

Collaborations have been established between Pharmacogenetic Research Network investigators (18), the NCI, the Cooperative Groups, and the Rikagaku Kenkyusho Center for Genomic Medicine in Japan (19) to use GWAS to find genetic variations of germline DNA associated with cancer treatment and prevention responses and adverse events. A recent GWAS from the Postmenopausal Breast Cancer Adjuvant Trial MA.27 found several single-nucleotide polymorphisms associated with musculoskeletal adverse events in women who received adjuvant therapy with aromatase inhibitors for early breast cancer (20). These novel

findings may lead to the prevention of musculoskeletal adverse events in women who receive these therapies, and they specifically illustrate the incredible opportunity to advance discoveries in personalized cancer medicine by conducting pharmacogenomic research using pooled trial data and specimens.

Federal agencies can ensure that collected specimens are available and are used to answer critical clinical questions most efficiently by 1) establishing mechanisms and common protocols that allow specimens to be pooled across studies and shared with outside investigators; 2) creating a searchable inventory of specimen collections, accompanied by annotated data for each patient, to facilitate their use; and 3) developing mechanisms to fund maintenance of biospecimen repositories and sustained long-term follow-up of trial participants, including cohorts created de novo across trials.

Answering future research questions requires a substantial amount of planning and coordination today. As much as possible, the most versatile DNA specimens should be collected for future research use (eg, blood samples may provide more analytic flexibility than saliva samples). Methods for specimen collection, storage, and handling should be standardized to provide consistently high-quality samples that can be pooled across studies. However, the samples alone are of little value without careful annotation of drug exposures, clinical outcomes, and demographics. Additionally, information concerning dietary, environmental, and other lifestyle factors should be collected to greatly add to the validity of studies. Currently, information concerning these variables is not consistently collected within clinical trials nor coordinated across studies. The development of new statistical methodologies is needed to harmonize, manage, and analyze these large and complex pooled datasets. The Breast Cancer Intergroup of North America has established systems and procedures for sharing specimens and has already conducted several collaborative pharmacogenomic research investigations. Lessons learned from their successes and challenges can help direct efforts for other cancer and clinical trial networks (21).

### **Pharmacogenomics and Pharmacoepidemiology in Observational and Population-Based Studies**

Recommendation 3 calls for the support of observational studies that identify clinical, sociodemographic, lifestyle, clinical, and genomic factors that influence treatment response and/or adverse events. Observational studies can be useful to validate clinical trial findings of predictive factors associated with treatment response and adverse events and to evaluate treatments in patients who were not represented in the clinical trials. Observational studies can be particularly important to assess rare adverse events and the impact of age, organ-system impairment, lifestyle factors, and other diseases on the effectiveness and safety of newly approved therapies.

In many situations, specimens and/or clinical and epidemiological data, such as comorbid conditions and lifestyle factors, may not have been collected in adequate numbers within existing clinical trials and correlative studies to answer important clinical questions. In these situations, observational studies can be helpful to discover and validate new associations. These studies may include analyses of 1) rare or long-term events, including toxicities and future outcomes of cancer; 2) effects or outcomes of off-label use;

3) drug–drug interactions; and 4) contributions of lifestyle, demographic factors, and other comorbid conditions. Observational studies would help to confirm the importance of genomic variations identified in cancer therapy trials, particularly when trials are underpowered, and also to study the impact of genetic variations in response to therapy and/or to study toxicities among diverse patient populations and ethnic groups that were not adequately represented in clinical trials.

There are several examples of how observational studies have been used to identify clinically important associations. One recent example involves the association of cytochrome P450 2D6 gene (*CYP2D6*) polymorphisms with outcome among women with breast cancer who were treated with tamoxifen. Retrospective analyses of clinical trials (22–27) showed that breast cancer patients who were classified as poor or intermediate metabolizers based on their *CYP2D6* genotype had unfavorable outcomes on tamoxifen. However, the clinical relevance was uncertain because of small sample sizes within studies and inconsistent quality and results across several clinical studies. Recently, Schroth et al. (28) published the first adequately powered study, an observational study of a cohort of 1325 breast cancer patients that showed a statistically significant association between *CYP2D6* genotypes and clinical outcomes. This study validated the previous retrospective clinical trials analyses and provides additional evidence for the clinical relevance of using *CYP2D6* genotypes to inform breast cancer treatment. A study by Ross et al. (29) that demonstrated that variants in the genes for thiopurine methyltransferase (*TPMT*) and catechol-*O*-methyltransferase (*COMT*) were strongly associated with hearing loss among children receiving cisplatin chemotherapy is an excellent example of the use of an observational cohort study design to identify the cause of an otherwise idiosyncratic adverse event. They analyzed candidate genes in an initial cohort of 54 children treated in pediatric oncology units, followed by a replication in a second cohort of 112 children recruited through a national surveillance network for adverse drug reactions in Canada. In an example of a pharmacogenomic observational study that examined factors related to survival, Chan et al. (30) analyzed a prospective cohort of 1279 men and women with colorectal cancer and found that regular aspirin use after the diagnosis of colorectal cancer is associated with a lower risk of colorectal cancer-specific and overall mortality, especially among individuals with tumors that overexpressed cyclooxygenase-2.

A comprehensive and coordinated research approach is necessary to translate promising findings such as these into clinical practice. The workshop participants recommended developing and supporting opportunities for the creation of new observational patient cohort studies that include standardized and uniform collection of comprehensive specimen and treatment data. These patient cohorts would be essential not only for measuring genomic factors and biomarkers within high-standard biospecimens but also for assessing health behavior and lifestyle factors during critical time periods, such as during and shortly after therapy. In addition, it would be beneficial to leverage existing population-based research studies and networks to answer questions that cannot be addressed through existing resources. Such efforts should include establishing sustainable cohorts of cancer patients; obtaining epidemiological, clinical, and biological data on study participants

over a number of years; and/or leveraging existing networks, such as the NCI-sponsored Health Maintenance Organization–Cancer Research Network (31), health maintenance organizations (32), and other private entities with electronic medical records through which to obtain information on prescription drug use.

### Pharmacogenomics in Basic Science

Recommendation 4 calls for support of basic pharmacological research on the pharmacodynamics and pharmacokinetics of drugs used in the prevention and treatment of cancer. There is a need to better understand complex pharmacokinetic and pharmacodynamic pathway mechanisms at early stages of drug development as well as after drug approval. This includes the study of the targets of cancer drugs, and their relationships with genetic variations that affect drug response because of differential gene expression, protein production, receptor-binding affinity, and/or enzyme level and activity. Functional analyses of the proteins encoded by genes identified in GWAS also will be valuable in clinically homogeneous case subsets. Such research will help to identify the genomic contributions to drug response and adverse events and will provide novel insight into mechanisms of drug action and disease pathophysiology.

There are a number of recent examples of the impact of pharmacokinetic and pharmacodynamic analysis on our understanding of variation of response to cancer treatment. Pharmacokinetic and pharmacodynamic evaluation of the *CYP2D6*-mediated metabolism of tamoxifen implicated endoxifen as the key active metabolite, leading NCI to begin development of endoxifen as an agent to be used alone in treating breast cancer (33). Pharmacokinetic and pharmacodynamic studies can also inform our mechanistic understanding of adverse events. As mentioned above, a recently published GWAS (20) identified three single-nucleotide polymorphisms on chromosome 14 associated with musculoskeletal adverse events in women receiving aromatase inhibitors. Functional analysis of these single-nucleotide polymorphisms indicates that they are associated with decreased T-cell leukemia/lymphoma protein 1A (*TCL1A*) expression related to estrogen exposure (20).

### Clinical Effectiveness, Utility, and Dissemination of Pharmacogenomics and Pharmacoepidemiology Knowledge

Recommendation 5 provides support for studies of clinical utility that focus on the effectiveness of pharmacogenomic applications in general clinical practice and the implications of incorporating these tests in representative patient populations and/or general populations. Translational research that moves pharmacoepidemiology and pharmacogenomic discoveries from basic science and clinical trials to the bedside has been limited at best. Research is needed to help clarify the levels of evidence that are needed for acceptable adoption of new pharmacogenomics technology into clinical practice. Although randomized clinical trials are gold standard for determining the efficacy of treatments, prospective and retrospective observational studies with high-quality phenotyping data might be adequate for the adoption of some diagnostic tests and certain treatment decisions. In addition to assessing immediate clinical endpoints, studies should incorporate longer-term outcomes, such as survival, patient-reported outcomes, and cost–benefit

analyses, as well as key factors influencing patients' decisions and preferences for cancer treatment. To address this need, under provisions for the National Institutes of Health in the American Recovery and Reinvestment Act, NCI recently funded seven large projects (34) for 2-year efforts that will advance methods for the evaluation of the clinical validity and utility of existing and emerging genomic personalized medicine applications in cancer control and prevention. These initiatives should enhance the clinical and population data infrastructure to support comparative effectiveness research initiatives in genomic personalized medicine.

Dissemination studies that focus on barriers and facilitators to wide-scale adoption of proven pharmacogenomic technologies or on the overuse or misuse of technologies that have questionable risk to benefit profiles should be supported. In addition, research on effective processes, such as clinical decision support tools, should be supported to integrate pharmacogenomic technologies into clinical practice. Furthermore, the existence of different practice settings, such as rural clinics, academic institutions, medical centers, should be taken into account as part of the strategy for enhancing the incorporation of pharmacogenomics information into regular clinical practice.

### **Bioinformatics**

Recommendation 6 supports the development of new bioinformatics methodologies and statistical expertise to process large volumes of data and to harmonize and combine existing samples, population information, and data. Linking pharmacogenomic and pharmacoepidemiology data, particularly the results of GWAS regarding the association of gene variants with adverse events, drug response, patient characteristics, and other data, will also be important. These activities will need to be coordinated with the new Biomedical Informatics Grid Health Consortium (35), NCI's cancer Biomedical Informatics Grid (36), Human Genome Epidemiology Network (10), and the PharmGKB (11).

### **Ethical, Legal, Social, and Data-Sharing Implications**

Recommendation 7 recognizes a need to implement specific and consistent procedures for data sharing and protection of confidentiality. The long-term follow-up of patients, the analysis of stored specimens for new purposes, and the sharing of information across investigations that includes sharing across government and private sector boundaries, bring new legal, ethical, and social challenges that must be addressed. Support is needed at all levels, including the development of educational resources to help institutional review boards better understand that the risks of collecting pharmacogenomics marker data on patients differ substantially from the risks of collecting data for other types of disease markers. Data-sharing policies will also be needed (especially for multinational collaborations), and appropriately flexible informed consent forms will be needed to ensure that patients have the opportunity to give or deny consent to use their biospecimens and other data in studies that may be conceived years—or potentially, even decades—after their original consent.

### **Training**

Combining two rather young fields, pharmacogenomics and pharmacoepidemiology, depends on the integration of genetics,

epidemiology, and pharmaceutical sciences, which may require additional training and the development of new skill sets. A successful investigator in these fields must be conversant in such disparate disciplines as pathology, statistical genetics, and information technology. Such expertise takes considerable time to develop. Recommendation 8 states that efforts are needed to expand transdisciplinary training programs in pharmacogenomics, pharmacoepidemiology, and clinical pharmacology. Fellowships and career development training grants at NCI, FDA, other federal agencies, and universities are needed to promote doctoral- and postdoctoral-level training to enable physicians and other researchers to obtain these skills.

### **Coordination and Partnerships of Public and Private Entities**

Last, workshop participants recommended that the PPWG continue its work to support, facilitate, and coordinate trans-NCI efforts to develop initiatives and activities in pharmacoepidemiology and pharmacogenomic cancer research that ensure the integration of the basic, clinical, and population sciences. To facilitate collaboration and avoid overlapping efforts beyond the NCI, it will be critical to identify ongoing efforts by other federal agencies, in the private sector, throughout the European Union, and globally to foster partnerships that may include the FDA, HMOs, pharmacy benefit providers, the CDC, the Centers for Medicaid and Medicare Services, the Agency for Healthcare Research and Quality, the Department of Defense, the Department of Veterans Affairs, and professional medical societies.

### **Summary of Workshop: Research Priorities**

The advancement of cancer pharmacogenomics and pharmacoepidemiology research has promise to facilitate the discovery and translation of research findings that will improve clinical decision making and increase cancer survival while reducing the harms associated with cancer treatment. The trans-NCI PPWG and participants of an NCI-sponsored Pharmacogenomics Workshop considered how best to foster cancer pharmacogenomic and pharmacoepidemiology research. Their ideas included ways to rapidly translate the results of bench research into medical practice and ways to test hypotheses generated from epidemiological and clinical investigations in the laboratory. Together, these complementary and interacting approaches will help us realize the benefits of a personalized approach to cancer treatment and prevention. As currently envisioned, a cancer pharmacogenomics and pharmacoepidemiology initiative will also encourage collaboration across disciplines and partner with other federal agencies with shared interests to leverage resources and knowledge. The research sponsored by such an initiative will improve our understanding of adverse drug events through systematic, rather than anecdotal, risk to benefit analyses; increase our ability to understand and monitor the effects of commonly used drugs on cancer risk; enable us to more efficiently track off-label drug use and its effects; improve cancer treatment and cancer prevention trial designs; improve postmarketing surveillance (particularly of new antineoplastic agents); and potentially reduce the cost of cancer care by matching treatments to patients most likely to benefit.

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## Funding

NCI sponsored the 2009 workshop and the Pharmacogenomics and Pharmacoepidemiology working group. The funding source has not dictated any of the content of this commentary.

## Notes

We gratefully acknowledge the contributions of many individuals with whom we have had discussions and who have been supportive of this effort. These include current members of the PPWG (Supplementary Material A, available online) and participants in the workshop (Supplementary Material B, available online). We particularly thank Dr Rochelle Long for her invaluable insight and contributions to this article and participation in the workshop. We also thank Ms Linda Anderson for her editorial assistance.

Dr Mark Ratain reports receiving royalties from the University of Chicago in regard to UGT1A1 genotyping and relationships with Bristol-Myers Squibb, Genentech, and Novartis. Dr Geoffrey Ginsburg reports business relationships with Cancer Guide Diagnostics, Inc, and Pappas Ventures. Dr Mary Relling reports receiving research funding from Sigma-Tau Pharmaceuticals and royalties from St Jude for licensing of patents related to TPMT and GGH polymorphisms.

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Margaret Hospital, University of Toronto, Toronto, Ontario (GL); Division of Clinical Pharmacology, Indiana University School of Medicine, Indianapolis, IN (DAF); Division of Preventive Oncology, German Cancer Research Center and National Center for Tumor Diseases, Heidelberg, Germany (CMU); Public Health Sciences Division, Fred Hutchinson Cancer Research Center, Seattle, WA (CMU); The Center for Health Research, Kaiser Permanente, Atlanta, GA (RLD); Office of Clinical Pharmacology and Biopharmaceutics, Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, MD (LJL, IZ); Center for Outcomes and Evidence, Agency for Healthcare Research and Quality, Rockville, MD (GR); Department of Cancer Prevention and Control, Roswell Park Cancer Institute, Buffalo, NY (CBA); Department of Pharmaceutical Sciences, St Jude Children's Research Hospital, Memphis, TN (MVR); Division for Clinical Research Resources, National Center for Research Resources, National Institutes of Health, Bethesda, MD (HX); University of Texas M.D. Anderson Cancer Center, Houston, TX (MRS).