Society for Clinical Data Management
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Data Basics

To advance excellence in the management of clinical data

A PUBLICATION SUPPORTED BY AND FOR THE MEMBERS OF THE SOCIETY FOR CLINICAL DATA MANAGEMENT, INC.

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Letter from the Chair

Nimita Limaye, PhD, CCDM

Dear Members,

Welcome to a bright and successful New Year! We have just closed 2010 on a successful note under the able leadership of 2010 Board Chair Ralph Russo. I greatly enjoyed working with Ralph this past year. His foresight, mature leadership and deep commitment added considerable value to SCDM. Thank you Ralph, on behalf of the entire organization!

Close to 700 new members joined the SCDM family in 2010. As part of the newly-launched student membership initiative, we also introduced nearly 150 new student members to our organization. In spite of the current global recession, SCDM has more than 2,600 members today! It is also notable that nearly one-fifth of our membership is international.

Other 2010 highlights:

- We ended the year with 580 CCDMs. One-fourth of these are international, with the majority from India, Canada and South Africa. This reflects the growing recognition of the value of CCDM® certification globally.
- We established collaborative educational partnerships with the U.S. Food and Drug Administration, Duke Clinical Research Institute, AHIMA, ACRP, CDISC and others.
- We collaborated with the Center for Pharmaceutical Publishing in Tokyo to release a Japanese translation of the GCDMP, our industry best practices.
- The focus on the changing role of the data manager and global outsourcing trends were demonstrated by new chapters in the GCDMP on Project Management for the CDM, and on Vendor Selection and Management. In line with this, a webinar and pre-conference tutorial on "Outsourcing Strategy and Methodology" were conducted as well.
- The Annual Conference was widely appreciated, featuring more than 50 speakers from across the globe. Special thanks to all of our sponsors and the 575 attendees who supported this event. Conference co-chairs Paul Clarkson and Charlene Dark, as well as the support team at EDI, attended to every detail to ensure a successful conference.

This year, we welcome three new members to the Board of Trustees: Jonathan Andrus, Jennifer Duggan and Meredith Nahm. They bring a diverse mix of expertise from software solutions, the device industry and academics. Departing the Board are Linda Talley, Vesna Zovkic and Debra Jendrasek. Thank you all for your service. We shall miss you!

This is expected to be a year of significant change for SCDM, with new globalization initiatives, partnerships and measures to diversify and examine the bigger picture so as to encompass the entire data value chain in the drug discovery and development process. Vice Chair Susan Howard, Secretary Carol Garvey, and Treasurer Gregg Dearhammer, all stalwarts in this industry, bring immense leadership to the Executive Committee, as does our executive director, Eloiza Altoro-Acevedo.

I am deeply honored and humbled to serve as the first international chair of SCDM, and would like to take this opportunity to sincerely thank the entire membership and the Board for the confidence they have placed in me. Five years in, my involvement with SCDM has been a rewarding experience. I have truly enjoyed every minute of it. SCDM is a professional and committed organization comprised of thoughtful, warm and capable people.

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This Issue

Letter from the Editors

Dear SCDM Members,

Welcome to the Winter 2010 Issue of Data Basics!

Just as technology has continually advanced to give us smart phones, high-tech gaming consoles and hybrid cars, there has long been a need for introducing medications with high specificity. This is even more important due to the idea that drugs with higher specificity can potentially lead to lower health costs and fewer adverse events if it can be reliably determined who will optimally benefit from a certain medication.

The concept of smart medicines is propelled by the discipline of pharmacogenomics, which can help biotech and pharmaceutical companies develop drugs for specific subpopulations. The use of metabolomics further serves this purpose by helping researchers find new markers for disease. While both pharmacogenomics and metabolomics may not seem like common topics among clinical data managers and in the mainstream of clinical trials, they are key disciplines which provide value and time savings for the overall drug development process.

Although this issue is leaner when compared to past issues of *Data Basics*, we think you'll find the articles interesting and the issue will provide you with the background for these disciplines.

As we move into 2011, we would like to encourage our readers to contribute new articles. Please check the SCDM website for our editorial calendar.

Please be sure to also check out the SCDM webinars and online courses scheduled throughout this year. A full schedule has been printed below. There are a wide variety of topics with some of the latest trends in our industry.

Happy New Year!

Sincerely,
Rehana Blunt and Lynda Hunter
Data Basics Co-Editors

Register at http://portal.scdm.org

2011 SCDM E-Learning

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2011 Online Course Offerings

Online Course	Dates
CRF Design	Jan. 10 – Feb. 4
Developing Data Management Plans	Feb. 7 – Mar. 11
Query Processing and Tracking/Database Updates	Mar. 14 – Apr. 8
Metrics and Identifying Data Trends	Apr. 11 – May 6
Processing Lab Data	May 9 – Jun. 3
SAE Reconciliation, Safety Review and Coding	Jun. 6 – Jul. 1
Database Lock and Randomization	Sep. 19 – Oct.14
Project Management for the Data Manager	Oct. 17 – Nov. 11

2011 Webinar Schedule

Webinar 11:00am Central; 60-minute presentation (30-minute Q&A)	Dates
What's New with ePRO Systems: FDA Updates and Regulations	Feb. 17
Adaptive Trial Design – What It Means for the CDM	Mar. 17
Using the CDISC Standards End-to-End in Clinical Trials	Apr. 14
Device Trial Strategies and the CDM's Role in Quality Assurance	May 19
21 CFR Part 11 for the Clinical Data Manager	Jun. 23
Biostatistics – What Every Clinical Data Manager Should Know	Sep. 22 & 29
Data Integration and the GCDMP: A New Chapter in Clinical Data Management	Oct. 20
The Role of Metrics in Clinical Data Management: Tracking Quality and Efficiency	Nov. 17

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Pharmacogenomics Overview and Impact on Data Management in Clinical Research

by Margarita Strand, Lead Clinical Data Manager, Oncology at Novartis.

Abstract

This article provides a brief overview of selected literature on Pharmacogenomics (PGx) as a branch of pharmacology, and describes methods of studying the genetic basis of patients' response variability to investigational compounds in clinical research with a focus on the data management aspects of clinical trials involving pharmacogenomics data.

Pharmacogenomics Definition

Pharmacogenomics (PGx) is the branch of pharmacology which deals with the influence of genetic variation on drug response in patients by correlating gene expression or single-nucleotide polymorphisms (SNPs) with a drug's efficacy or toxicity.[1] Single nucleotide polymorphisms, or SNPs (pronounced "snips"), are Deoxyribonucleic Acid (DNA) sequence variations that occur when a single nucleotide (A,T,C,or G) in the genome sequence is altered.[5]

Although pharmacogenomics is broader in scope and refers to the complex interactions of genes across genome, the terms 'pharmacogenomics' and 'pharmacogenetics' are often used interchangeably in the literature.[2]

History of Pharmacogenomics and Current Status

Rapid identification of tens of thousands of human genes and hundreds of thousands of DNA variations that might influence disease susceptibility has spawned a new field — pharmacogenomics.[3] Pharmacogenomics is an offspring of pharmacogenetics. The history of pharmacogenetics dates back to the 1900s.[4]

Over the past few decades, due to such major accomplishments as the completion of the Human Genome Project[6] in 2003, which has provided a blueprint of the DNA present in each human cell, rapid progress has been made by using genetics to identify the molecular cause of human disease. Genomics research is now focusing on the study of DNA variations that occur between individuals, seeking to understand how these variations infer susceptibility to common diseases such as diabetes or cancer.[7]

Application of PGx in Clinical Research

The two major goals for clinical application of PGx are:

- Ability to predict patients who are at high risk of toxicity in an effort to prevent serious adverse events (SAEs) and ensure safety
- Ability to predict patients who are most likely to obtain the desired therapeutic effect from the drug in an effort to increase efficacy[8]

Both of these define possibilities for incorporating genotyping into each phase of a clinical trial.

With recent advancements in the field of PGx, genetic factor can now be considered an intrinsic or predictable factor affecting drug response and can be added to the other intrinsic factors including age, gender, race/ethnicity, disease state, organ dysfunction, etc.[8]

230 clinical trials involving pharmacogenomic testing have been registered with ClinicalTrials.gov website[9] as of October 1, 2010 demonstrating widespread use of pharmacogenomics in clinical research.

PGx in Oncology Research

Tumor biopsy allows for direct analysis of abnormal tissue, which explains why PGx

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Letter from the Chair

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I know that this is just the beginning, and I shall seek your continued support to help drive the strategic vision that we have set to make this a truly global organization of considerable repute.

Once again, wishing you all a sparkling and successful New Year,

Nimita Limaye, PhD, CCDM
2011 Chair
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analysis of efficacy in cancer research is well ahead of other complex diseases that must solely rely on genetic association studies.[11] For example, patients with metastatic colorectal cancer (mCRC) whose tumors carry wild-type version of KRAS gene respond to Panitumumab (Vectibix) better than patients whose tumors carry a mutated form of KRAS.

A commercial test – TheraScreen's K-RAS Mutation test – was approved in Europe to detect seven mutations found in many cancer types and is now used to predict Vectibix efficacy.[11] Patients with non-small-cell lung cancer (NSCLC) respond favorably to Gefitinib (Iressa®)—if they have particular mutations in the tyrosine kinase domain of the epidermal growth factor receptor gene (EGFR) of their tumor. The findings suggest there is no need to try this anti-cancer drug in patients not having this tumor EGFR genotype.[14]

Stratification of Research Subjects

Figure 1 illustrates the current state of the drug development process where only a limited number of patients are treated with a specific drug for any given disease due to adverse events. Of those patients who are receiving the drug, not all respond.[10]

The future of drug development is based on genotype-induced subject stratification and is presented in Figure 2 where each sub-group is represented as having a drug available that is tailored to their genotype with the benefit of reduced adverse events.[10]

Regulatory Perspective

With active support from regulatory agencies, PGx is also becoming an important aspect of drug labeling so that groups of patients who are most likely to respond, and less likely to suffer adverse events, can be identified in practice.[11]

Increasing interest from regulatory authorities on potential applications of PGx has raised the awareness of the use of PGx data in the drug discovery and development. The Food and Drug Administration (FDA) has published 'Guidance for Industry Pharmacogenomic Data Submissions'. It was generated specifically 'to facilitate scientific progress in the field of PGx and the use of PGx data in drug development'.[12] Not only does it provide guidance on PGx data submission requirements, but also encourages voluntary submission of data for discussion with the agency's newly formed Interdisciplinary Pharmacogenomics Review Group (IPRG).[12]

ICH has also issued Guidance for Industry E15: 'Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories'.

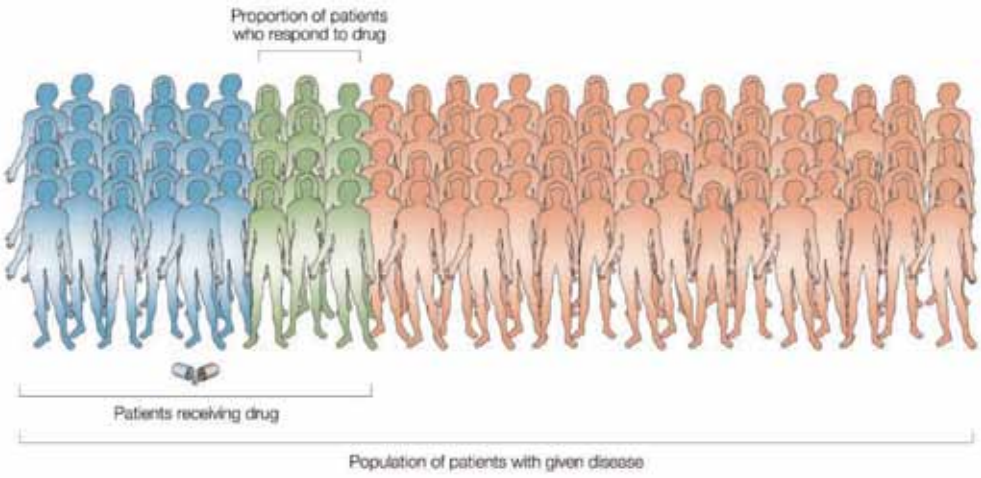

Figure 1. Current state of drug development process[10]

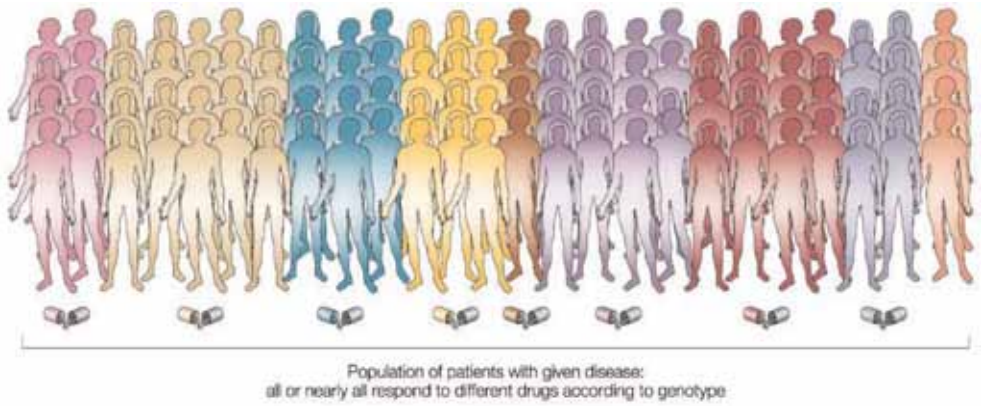

Figure 2. Future state of drug development based on genotype-induced subject stratification[10]

The willingness of regulatory agencies and pharmaceutical companies to adopt a collaborative approach to PGx will be a key factor in moving PGx forward, as well as the agency's approval of validated pharmacogenomic tests.[12]

Data Management Aspects of Clinical Trials with PGx Data

Several aspects of a clinical trial involving PGx data should be considered from the Clinical Data Management perspective during study start-up phase (Table 1) and evaluated throughout the course of the study with the implementation of quality assurance and quality control measures to ensure high quality data.

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#	Aspect	Clinical Data Consideration from Data Manager's (DM) Perspective
1	Study Protocol	Data Manager should thoroughly review sections in the Protocol related to PGx, ensure understanding of the sample collection methodology for PGx studies and analysis, evaluate impact on the Case Report Form and clinical database design (see also CRF section below).
2	Data Management Plan (DMP)	Data Manager should incorporate genetic testing component and genetic data handling into the DMP as well as define the flow of the genetic data and its integration into the overall data management process.
3	Case Report Form (CRF)	Study specific CRF pages collecting genetic testing data need to be designed. The use of the data for statistical analysis purposes needs to be evaluated, discussed with the trial statistician and aligned with the Statistical Analysis Plan (SAP).
4	Subject's Eligibility Criteria	Inclusion and exclusion criteria need to be carefully evaluated to account for the subject's genotype. Receipt of results of mutational/genetic analysis from the analytical laboratory prior to Baseline visit becomes essential for evaluation of eligibility criteria. Potential impact on the speed of subject's recruitment needs to be evaluated and discussed with the Clinical team.
5	Clinical Database Design	Variable names, formats, codelists and dataset structure associated with genetic data need to be defined. Appropriate annotations need to be created by the programmer in the Annotated CRF and database design specifications.
6	Data Validation Checks	Edit checks intended to detect potential errors and discrepancies in genetic data need to be developed, programmed, tested and implemented.
7	Randomization Mechanism	Depending upon the system used to randomize the subjects into the study (e.g. Interactive Voice Response System (IVRS), Interactive Web Response System (IWRS), etc.) randomization scripts need to be written, programmed, thoroughly reviewed and tested to ensure that, for example, subject with genotype A is assigned to treatment arm A, and subject with genotype B is assigned to treatment arm B (as defined in the Study Protocol). Availability of mutational/genetic analysis results from the analytical lab prior to the Baseline visit becomes essential for subjects' stratification and assignment to the appropriate treatment arm.
8	External Data Handling (non-CRF)	Data transfer specifications (DTS), frequency, timing and method of genotype data transfer from the external vendor (analytical lab) need to be defined and agreed upon. Test data transfer should be checked for compliance with database structure defined in the DTS.
9	Data Review and Cleaning	Method and extent of PGx data review, cleaning and reconciliation as well as query management should be defined in the DMP. Data listings/ reports necessary to review the PGx data from the DM perspective as well as layout of the Patient Profiles/reports used by Clinical and Safety teams to review the safety and efficacy data in correlation with the subject genotype variations need to be defined and programmed.
10	Adverse Events / SAEs	Correlation between safety signals and genotype should be evaluated (particularly for SAEs) during safety monitoring and AE classification.
11	Clinical Database Lock	Data Manager needs to incorporate items related to PGx data into the clinical database lock checklist and ensure the checklist is followed.
12	Training	For in-house trials, the internal study team personnel are trained on the process of collecting and handling PGx data. For outsourced trials where a Contract Research Organization (CRO) is involved, clear understanding of the roles & responsibilities by the CRO's DM team with respect to PGx data handling should be ensured.

Table 1 – Data Management Aspects of Clinical Trials with PGx Data

Conclusions

Pharmacogenomics can provide substantial efficiency in clinical research by facilitating the conduct of smaller clinical trials while targeting groups of patients with similar genetic background. The approach of determining the genotype/phenotype relationship in individual drug response will provide physicians and researchers with the key information that allows them to precisely prescribe or design the right drug, at the right dose, for the right patient.[13]

Blending the components of genetics and pharmacology, PGx has created a new paradigm in the pharmaceutical landscape.[15] With a widespread adoption in clinical research, PGx has a potential to become a core component of conventional drug development in the near future. Considering the important role of Clinical Data Management, Data Managers should be prepared to handle PGx data by means of acquiring knowledge about this subject, welcoming opportunities to learn and gain experience, leveraging technology, and developing and implementing good pharmacogenomics data management practices.

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Pharmacogenomics and Metabolomics

by Nimita Limaye, PhD, CCDM, VP and Global Head, Strategic Data Services and Medical Writing, SIRO Clinpharm Pvt. Ltd.

Pharmacogenomics and metabolomics are two of the key drivers of the massive "omics" explosion. Systems biology aims to facilitate a comprehensive analysis of the interactions of complex biological systems using key tools such as pharmacogenomics and metabolomics to develop predictive models of human disease. Integrated analysis of organ and system-level responses using innovative computational analytical techniques would help identify biomarkers and design clinical trials, factoring in both genotype-phenotype as well as genotype-envirotype relationships. The application of health informatics to the data overflow resulting from the application of such technologies would drive faster, more focused and targeted drug discovery, reduce healthcare cost and pave the way for personalized medicine.

Pharmacogenomics and metabolomics, along with the other 'omics,' such as epigenomics and neurogenomics, are some of the tools which are spearheading the new age of predictive, preventive and personalized (PPP) medicine.

Pharmacogenomics is a branch of pharmacology which deals with the influence of genetic variations on drug response in patients by correlating gene expression or single-nucleotide polymorphisms with a drug's efficacy or toxicity.[1] Thus, it aims to optimize drug therapy with respect to the patient's genotype to ensure maximum efficacy and minimize adverse effects. It follows a polygenic or genome-wide approach to identifying genetic determinants of drug response, as opposed to pharmacogenetics which examines single gene interactions with drugs. It is important to remember that while the number of polymorphisms in genes encoding drug-metabolizing enzymes, drug transporters and drug targets, as well as disease-modifying genes that have been identified continues to increase, most drug effects and treatment outcomes are determined by the interplay of multiple genes, and this is where pharmacogenomics comes into the picture.

These technologies are not only being used to treat critical illnesses like cancer, cardiovascular disorders and diseases such as HIV, tuberculosis, asthma and diabetes. A good example is the research on Warfarin (an anticoagulant) which has shown that two genes impact the optimal dosing of Warfarin. These genetic factors account for 30 percent to 35 percent of the variability in the dosing, while clinical factors are responsible for only 17 percent to 21percent.[2]

Pharmacogenomics is also being applied to 'theranostics' – the merger between therapeutics and diagnostics in the form of a DNA test to predict a patient's response to the drug – and has been effectively used to select patient subpopulations for clinical trials, for example in the K-ras test with Cituximab and EGFR test with Gefitinib.[3] Similarly, gene signature microarrays to relate patterns of gene expression with specific clinical outcomes, such as the 70-gene signature "Mammaprint", a U.S. Food and Drug Administration-approved tool commercialized by Agendia, are being used for breast cancer prognosis and have been reported to be 77 percent to 81 percent accurate.[4] This new set of molecular diagnostic tools can be used to individualize and optimize drug therapy.

Pharmacogenomics not only serves to identify new targets for the development and use of drugs in specific, identifiable subpopulations, but also plays a significant role in reducing the incidence of adverse events by excluding patients who are likely to suffer such events. This will probably serve to lower the cost of health care and make pharmacogenomics an invaluable tool for predictive, as well as preventive, medicine.[5]

This could be done by identifying polymorphisms that predispose patients to adverse drug effects, possibly by obtaining genomic DNA from patients entered on large Phase III clinical trials of a new agent, and then retrospectively searching for polymorphisms that predispose a small subset to toxicities.[6] Thus, predictive medicine would involve mapping the future health history of an individual and will mandate the cost-effective and swift sequencing of the human genome. This is not merely left to one's imagination as IBM has announced that it is in the process of developing a DNA chip that could be used in a handheld medical device on which patients can deposit a sample to get their DNA read in a matter of seconds or minutes.[7] This would cost between $100 to $1,000. The time frame of this project is three years and it intends to make personalized medicine affordable and quick.

Metabolomics is the "systematic study of the unique chemical fingerprints that specific cellular processes leave behind."[8] It is the study of the metabolome, the entire metabolic content of a cell or organism at a given moment. The metabolome represents the end products of gene expression. While transcriptomics (mRNA gene expression data) and proteomics (the use of a proteomics toolkit to facilitate biomarker profiling) analyses do not tell us the whole story

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Pharmacogenomics and Metabolomics

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of what might be happening in a cell, metabolic profiling can give an instantaneous snapshot of the physiology of that cell. Metabolomics attempts to tabulate and quantify all the small molecules within a sample and to find new markers for disease or metabolite patterns as indicators of nutritional status. A metabolic signature obtained from body fluids or tissues would serve as a metabolic footprint to assess individual health and disease risk, in a manner similar to DNA fingerprinting.

Metabolomics is an offshoot of genomics and proteomics, as it allows for the evaluation of both genotype-phenotype as well as genotype-envirotype relationships and is being used in pharmacology, pre-clinical drug trials, toxicology, transplant monitoring, newborn screening and clinical chemistry.

The human genome has now been fully sequenced and is freely accessible. While approximately 2,900 endogenous or common metabolites are detectable in the human body, metabolomics is yet to mature to that level. The Human Metabolome Project is a $7.5 million Genome Canada funded project launched in January 2005. It aims to provide insight into drug metabolism and toxicology, providing a linkage between the human metabolome and the human genome.[9]

Genetic heterogeneity does not consider environmental and other external contributions to individual's biological condition; however, the metabolic phenotype of an individual can be statistically modeled prior to drug administration and can be used to predict post-dose pharmacokinetic response. Systems biology builds upon the reconstruction of biological systems using metabolomic data and uses these to derive testable hypotheses and the predictive models. Changes in the concentration and flux of the metabolites allow for a better understanding of regulatory mechanisms and metabolic networks. This helps further interpret whole cell behavior.

Detailed studies on metabolomics have been conducted primarily on microorganisms and plants. There has been limited work done on animals or humans, with the main focus being on biofluids, rather than on cells. Evaluating changes in metabolic profiles will play a key role in performing an integrated analysis of gene function and its relationships to phenotypes, and would have a significant impact on biomedicine.

Drug screening libraries typically screen for desirable pharmacokinetics characteristics and biophysical descriptors of drug likeness or lead likeness. However, in order to enter cells, drugs require solute carriers akin to naturally occurring intermediary metabolites (endogenites) and are likely to interact in a similar manner to them. Cheminformatics molecular descriptors are now being used to assess metabolite-likeness which is being used as a criterion in the design and selection of pharmaceutical drug libraries.[9]

While mass spectroscopy and nuclear magnetic resonance are well-established tools for metobolite analysis, the rate-limiting step could be ready accessibility to metabolomics databases.

At the end of the day, accessibility to biobanks (repositories of biological samples such as DNA or tissues), with different kinds of information attached to samples allowing for mapping to distinct population subtypes, would allow one to correlate data. Data such as frequencies of markers like SNPs (single nucleotide polymorphisms), using automated molecular techniques, as well as the necessary bioinformatics tools, gene function, and identifying markers that might play a role in the aetiology of common diseases.

The three major publicly available databases that serve as central repositories for DNA and protein data are GenBank, maintained by the National Center for Biotechnology Information (NCBI), and DNA Databank of Japan and European Molecular Biology Laboratory (EMBL), maintained by the European Bioinformatics Institute. Similarly, data from the Human Metabolome Project will be freely accessible in an electronic format to all researchers through the Human Metabolome Database and all compounds will be publicly available through the Human Metabolome Library. Other comprehensive metabolomic databases include BiGG, SetupX, BinBase and SYSTOMONAS; whereas some drug databases include DrugBank, Therapeutic Target Database (TTD), PharmGKB, STITCH and SuperTarget. For example, PharmGKB contains data on more than 20,000 genes, more than 3,000 diseases, more than 2,500 drugs and more than 53 pathways. It also has detailed information on 470 genetic variants (SNP data) affecting drug metabolism, and helps relate genetic variations in individuals to differences in reactions to drugs.[11]

Thus, enterprise data management solutions and innovative computational analytical techniques are required to integrate all levels of biological data organization from source-to-outcome continuum to allow for the cost-effective analysis of data using a systems biology approach.

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Pharmacogenomics and Metabolomics

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Personalized medicine is about getting the right treatment for the right patient at the right time. Its success lies with the effective integration of pharmacogenomics, molecular medicine (including genetic and genomic sequencing, metabolomics, and proteomics) and health information technologies. Health informatics is defined as the intersection of information science, computer science and health care, which will potentially allow for molecular data to be linked to other health information, primarily by way of electronic medical records that include both physician and patient input.

In 2003, Hewlett-Packard formed a partnership with Partners Health Care in an effort to accelerate clinical genomics and advance the concept of individualized medicine by integrating genetic knowledge into the healthcare system. Microsoft partnered with more than 35 other organizations and institutions to form the BioIT Alliance, an alliance that is working to advance translational and personalized medicine by better integrating science and technology into healthcare. Microsoft has also developed a software platform, called Amalga, that will help advance personalized medicine.[1] This can be used to "assimilate large quantities of diverse data, including electrocardiograms, magnetic resonance imaging scans, dynamic angiograms, ultrasound images and ultimately, genomic information providing a visual gateway for instant access to the information, and allowing researchers to make and prove their hypotheses within minutes instead of months."

Phase I volunteers are routinely screened for drug metabolizing enzyme (DME) polymorphisms.[12] This screening is increasingly performed routinely at many pharmaceutical companies and patients enrolled in Phase II and Phase III clinical trials are being genotyped to correlate efficacy with genetic markers. Finally, the effective application of pharmacogenomics and metabolomics in the clinic will be based on the reproducible correlation of these data with data obtained from other established clinical measurements.

To quote Henig, from a 1989 *New York Times* article, "In the not-so-distant future, we can expect to walk into a physician's office for an annual physical and walk out with a blueprint of our genetic inheritance – and with the knowledge of the most likely cause of our own death."[13] ■

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***Nimita Limaye, PhD, CCDM,** holds a doctorate in biotechnology from Pune University and is currently working as VP and Global Head (Strategic Data Services & Medical Writing) at SIRO Clinpharm Pvt. Ltd. In her current role, she contributes to winning and establishing key engagements, ensuring sustainability and profitability and driving strategy for engagements across clinical data management, biostatistics and programming and medical writing. She has also been trained as a black belt in Lean Six Sigma and plays a key role in driving operational excellence. She is 2011 Chair of the SCDM Board of Trustees.*

Trends in Clinical Data Management Due to Growing Dissatisfaction with EDCs

by Mitch Scurtu, Owner, Gobal Technologies

A growing dissatisfaction in the pharmaceutical and biotech industries with current electronic data capture sytems (EDCs) on the market can be summed up along three directions:

- Quality of clinical databases
- Cost and time to deliver a quality database
- Inability to accommodate large-scale data management operations.

Quality of clinical database

Current EDCs on the market are mostly, if not exclusively, query-based data management systems. A small fraction of all errors in a database are cleaned or "prevented" up-front. The bulk of errors are cleaned with edit checks/queries in the back-end, after the data has been entered in the database. This situation is most likely to be overwhelming to data managers. You have many thousands or even millions of data points in the database. Edit checks are looking for errors in the database with a hit or miss rate of, at best, 50 percent. Out of the typical nine types of errors in a clinical database, edit checks can catch, at best, three to four types of errors. It is like the proverbial looking for a needle in a hay stack. If it happens that the errors are to be cleaned at the end of the study, this data cleaning job can become unreasonable, given timelines.

In the good old days, errors in a clinical database were measured by finding discrepancies between final SAS datasets and source documents from the clinic. Error rates were assessed consequently. Currently, EDCs cannot cope with the many errors in the database and fall back on measuring the quality of clinical databases with query rates (i.e., queries/page). If there are few queries per page, the quality of the clinical database is concluded to be OK. Some flows in this way of thinking are:

- What is an OK database? What is the quality assurance? Quality is, and must be, a measurable entity. General statements about the quality of a clinical database are less convincing.
- Edit checks are programmed upfront and tested on "clean" and "dirty" mock data to make sure the edit check is firing on errors, but not on clean data. In the back end we are dealing with real life clinical data, which is a dynamic entity and may or may not conform to whatever mock test data was generated upfront. Continuous reviewing and editing and changing of edit checks as real data is accumulating is at best a time consuming and difficult job to coordinate for most of the EDCs.
- What about the errors the edit checks did not catch? How much of the errors did the edit check not catch and how are these errors playing into the quality of the clinical database?

As far as I am aware, EDC vendors do not provide the client with positive numerical assessment of clinical databases the way we were doing it with quality certificates bearing among others, the error rates. You were looking at overall error rates per database, error rates per SAS data sets, error rate for critical data, which of course has to be zero. Validating the EDC system, training all personnel, and validating EDC processes are all parts of monster processes that are supposed to be conducive to the quality of clinical databases and supposed to replace a plain and direct measure of the quality of a clinical database. Those have many parts and are a poor predictor of the resulting quality of the database.

Cost and time to deliver a quality database

In a recent Phase IIB/Phase III study we worked in one of the top EDCs at a top contract research organization. Halfway through the study, we had 52,000 queries. As the industry cost for one query resolution is around $100, the cost of cleaning the 52,000 queries was $5.2 million. The whole data management budget for the study was $320,000. Four managers in charge of this study left the CRO successively, because they felt at a loss in attempting to fit the $5.2 million cost into a $320,000 budget. Upper management practice in this case is to shift the cost of cleaning clinical data to other functions like clinical, medical, or clinical site costs and claim data management a successful operation, staying within its budget. Obviously, upper management is doing the next best thing they know of.

Needless to say, time to clean the database, performing all QC, QA operations, locking database and delivering clinical data to the client was delayed by months and the blame and responsibility was evenly spread to all participating functions in the study. The client had to quietly bear the consequences, since all clinical, site management, data management and statistics functions were outsourced to us.

Inability to accommodate large scale data management operations

More than 50,000 queries half way through the study with each query having its own resolution cycle of theoretically five to 10 days, and practically two to six weeks, made for complicated, at times impossible, coordination work.

Add to this one or more additional studies and the job of simultaneously cleaning up databases becomes a nightmare, if not impossible. Pharmaceutical companies with hundreds of active studies running simultaneously cannot expect that a single CRO can take care of all their studies. Therefore, they are distributing their clinical trials among multiple CRO operations. More recent, pharmaceutical companies apprehensive about CRO performance are outsourcing less than full data management

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Trends in Clinical Data Management Due to Growing Dissatisfaction with EDCs

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services to CROs. They are outsourcing functions like programming edit checks, testing edit checks, building data entry screens, developing Case Report Forms (CRFs), and entering data into a database.That is what Nelson Lee, at the Society for Clinical Data Management, noticed in his review of some lessons learned from building a functional service provider partnership, published in *International Clinical Trials* in May 2010. Growing dissatisfaction of pharmaceutical/biotech companies and a lack of trust in the CROs' capabilities of handling full data management services in the current query-based EDCs, forced the sponsor companies to scale back their expectations of what a CRO can deliver.

Current EDC systems on the market are query-based systems and are therefore not capable of accommodating large-scale data management operations.

Trends in Clinical Data Management

Growing dissatisfaction with current query-based EDCs on the market is transforming traditional CROs into functional service providers. Everything that does not work with complex and complicated query-based EDCs is pushed off to the coordination nightmare of functional services provision. The trend of introducing query-based EDCs seems to be a bust, and a new cycle of thinking and acting in the direction of new solutions to the clinical data management puzzle is underway.

Both pharma and the EDC vendors are recognizing this trend and are attempting to "retool". Major pharma companies are discretely inquiring into the intelligent data management model, which some of them had in their operations more than 10 years ago in the form of homegrown data management systems. CROs, unhappy to be given less of a full data management service contract, are rethinking their options. The top CRO company is eager to re-introduce the intelligent data management model. More and more, EDC vendors are involving in their operations and especially in their names features. One EDC vendor even calls its EDC *IDAM*, which stands for intelligent data acquisition and management. Another EDC vendor and CRO service provider is calling its EDC *IDC* – for intelligent data capture.

What is the significance of "intelligence" and how is this making life of clinical data managers more tolerable?

Intelligence-based data management systems are intent on preventing errors entering clinical databases rather than catching them at the back end after data enters databases. This concept goes back to the intelligent data management model. Theory of this model draws heavily on the science of quality known in engineering, banking and retail. This theory deals with identifying the error types in a clinical database, identifying the sources of these errors, and teaching how to develop intelligence to contain error sources and specific ways of preventing all mechanical types of errors. Extensive research in the intelligent data management model identified nine typical errors in a clinical database and three major error sources, which are all study independent. Eight of these typical errors are mechanical errors (some data managers like to call these errors stupid errors) and one type was a logical error. Logical errors are defined as errors that require some clinical and/or medical reasoning to be resolved. Progress has been slow in developing a complete intelligence structure to prevent the eight types of mechanical errors and contain the three major error sources. This is the reason why pharma companies and major CROs involved in the early promotion of the intelligent data management model yielded to the introduction of query-based EDC more than 10 years ago.

However, the intelligence infrastructure is now a completely mature and known entity, capable of delivering high quality databases with initial error rates of 0.1 percent to 0.4 percent. An initial error rate is designated as the error rate measured as discrepancies between SAS data sets and source documents from the clinic at the time the data has past data entry. For non-critical clinical data, this is already acceptable quality for the U.S. Food and Drug Administration. Simple data entry into a database via an intelligent data management model EDC is delivering FDA-acceptable quality databases. Logical errors are made by human intelligence and, therefore, machine intelligence cannot handle them. Logical errors will have to be cleaned out of the database the old-fashioned way by manual review. The good news is that statistically, logical errors are only a small fraction of all the errors in a database (0.4 percent or less). Bad news is that logical errors are the most important errors, which can make or break a study. Clinical databases worked in an intelligent data management model EDC are typically high quality databases delivered at a fraction of the cost typical for query-based EDCs.

Example: For a Phase I study, data management services was quoted at $80,000 in a typical EDC; same study was quoted in an intelligent data management EDC at $5,000. Needless to say what the client's preference was.

At the back end of a database worked in an Intelligent Data Management EDC, there are only logical errors to be cleaned, therefore time to lock is greatly reduced. And because there are no edit checks to be programmed and no queries to contend with in an intelligent data management EDC, it is ideally suited for large-scale data management operations. ■

Ethical Issues in Pharmacogenetics

Carol Isaacson Barash, PhD, Principal, Genetics, Ethics & Policy Consulting

Pharmacogenetics is the study of how genes influence an individual's response to drugs. Though the field would seem to be brand new, it is really half a century old. In the 1950s, scientists first identified deficiencies in enzymes that explained adverse reactions to drugs and that these deficiencies could be inherited.

For example, early research showed that 10 percent of African American men serving in the Korean War became anemic after ingesting an antimalarial drug, which rarely caused problems for Caucasian soldiers. Pinpointing the cause took years of study:

- The anemic reaction was determined to be caused by a variation of the G6PD gene, and this variation was found to be common among people of African descent but not so among Caucasians.
- It was later discovered that the normal form of the gene makes an enzyme that helps protect red blood cells against certain chemicals. Lacking that protective effect, those with the variant form are vulnerable to deleterious effects.
- Since that time, numerous other enzyme variants have been identified and found to cause adverse reactions. Such adverse effects were identified, until recently, by trial and error methods. Specifically, drugs were administered, and an individual's metabolism of that drug was tracked by recording the amount of by-product in their urine.

The Human Genome Project has enabled us to identify the molecular composition of the enzymes in question so that we can study correlations between genotypic (gene trait) and phenotypic (physical trait) variability. These advances will increasingly enable us to detect individuals who are likely to experience adverse reactions to medicines without having to use potentially dangerous methods of trial and error.

In coming years, we are likely to learn that particular single nucleotide polymorphisms (SNPs) are associated with sensitivities or resistances to chemical compounds in the environment. Scientists are now rushing not only to identify common SNPs, but to determine what drug effects can be correlated to them. This knowledge is enabling "personalized medicine," or the ability to tailor therapy for positive efficacy and safety, thus avoiding trial and error prescriptions and improving patient care.

Pharmacogenomics is a recent offshoot of pharmacogenetics with a broader scope. For example, it attempts to understand not only the molecular composition of genetic variants associated with drug response, but also the behavior of those variants, including how those genes affect drug receptor sites. Pharmacogenomics is enabling drug manufacturers to develop therapeutic agents that are targeted to receptors and designed to reverse, or dramatically mitigate, the source of the health problem. Gleevac, one such smart drug, has demonstrated stunning success in fighting chronic myeloid leukemia. Thus, the ability to profile a patient's gene variations can guide both the development of new drugs, as well as the selection of treatment protocols that will more likely minimize harmful side effects and ensure more successful outcomes.

Ethical Issue #1: "Good" or "Bad" Allocation of Scarce Resources?

Many believe that pharmacogenomics, like other new fields spawned by the Human Genome Project, represent a misallocation of resources. Rather than embark on learning how genes indicate a predisposition to disease and developing cures and enhancements, or experimenting with ways to change the human germ cell, global efforts should be spent on solving more urgent problems facing humanity, such as global famine or accessibility to potable water.

Others contend that pharmacogenomics, in particular, offers enormous potential for clinical benefits to patients, as well as economic benefits for health care delivery. The arguments in favor of pharmacogenomics include:

- In the United States alone, adverse drug reactions are thought to kill about 100,000 hospitalized patients annually. It is believed that many of these reactions are due to genetic variants and thus many of these deaths can be avoided by testing people for adverse drug response before administering drugs. However, the science and technology for such tests are in their infancy.
- Another 2.2 million patients incur serious, non-fatal reactions. Physicians, as stated in their Hippocratic Oath, are obligated to do no harm. Can this obligation be fulfilled when the information available to physicians about how particular medicines will fare in their patients is so meager? At present, physicians generally have no way of knowing in advance whether the drug they prescribe will or will not cause an adverse effect in their patients.
- This situation is further compounded by the fact that most adverse drug reactions result from the fact that medicines are "a one-size-fits-all." In other words, although medicines are taken in different dosages depending on symptoms, patient

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age, weight and other clinical factors, these criteria may not be adequate to ensure that a particular medicine will be safe and effective for a particular individual. Until recently, there has been no alternative to either developing or prescribing medicines. Pharmacogenomics promises to take the guesswork out of developing and prescribing safe and effective drugs.

Ethical Issue #2: What is a fair distribution of burdens and benefits in developing the field of pharmacogenomics?

Monies and people (as research subjects and as researchers) will develop the field to the point that customized medicine will be possible. Who will benefit?

- The availability of this new technology may be initially costly, and thus accessible only to those wealthy enough to pay for both the test and the designer drug best suited to them. Yet, the cost will likely diminish so as to become affordable to most. However, will lower costs influence a person to submit to the required genetic testing, thus creating threats, if not violations, to one's autonomy (the basic tenet of bioethics)?
- Researchers who have investments in companies competing in their field may be in a conflict of interest if they are conducting research for such a company. Substantial concerns about conflicts of interest as both a threat to quality research, as well as to the well being of research subjects, have abounded for decades.[1]
- A recent study found that policies governing conflicts of interests at major medical institutions varied considerably in both disclosure requirements and the nature of permitted academic-industry relationship. This opens the door to the possibility that an interest in financial gain could overpower an interest in either achieving valid research or protecting the well-being of subjects.[2]
- There are several examples in the history of medical research where the patient population standing to benefit from advances (i.e., people who have donated their time, bodies, and hearts to research) though compensated per standard National Institutes of Health (NIH) terms, did not receive the anticipated medical benefits because new therapies were unaffordable when they became commercially available, or not covered by insurers. The following examples illustrate this:
  - Numerous sufferers of Gauchier Disease who helped companies develop safe and effective treatment (clinical research), were denied access to treatments by insurance companies that refused to cover the high-cost therapies. These patients could not afford to pay costs out of their own pocket.
  - A Canavan's Disease support group has been instrumental in helping a company develop treatment by raising research funds as well as supplying researchers with willing research participants. The group is suing research facilities, not for financial return on investment, but for the opportunity to play an active role in furthering research/treatment goals.[3]

Ethical Issue #3: Will individualized medicine be used ethically?

Knowing if a person will respond to a drug in ways that are safe and effective for that individual will enable patients to avoid medications that are dangerous or ineffective for them.

This is not to say that genes are the only key to cures. Environment plays a role, too. Dietary and lifestyle behaviors are still likely to affect the safety and efficacy of medicines for particular individuals. In addition, variation in drug response is not limited to micro polymorphisms.

Environmental factors also play a role (such as sun exposure, drug/drug interaction, drug/food interaction). However, scientists are poised to uncover why the metabolism of particular individuals absorbs and dispels pharmaceuticals in a particular manner.

Consider the following hypothetical clinical scenario as illustrating some of the ethical issues that can arise in clinic:

- A 42-year-old man of Scandinavian descent presents to his physician with a general feeling of malaise.
- Five years previously he was diagnosed with high serum cholesterol, which he attempted to control with a regimen of exercise and dietary regulation, with no success. His physician then prescribed for him drug therapy.
- Before agreeing to take the prescribed medication, the patient retrieved volumes of information from the web, including, but not limited to, peer-reviewed journal articles about his condition and his physician's first choice drug.
- After six months of therapy there was only a modest lowering of cholesterol levels, so the medication was changed. After nine months on the second medication, there was still no marked effect.
- By the time the patient was able to see his physician again, a newer therapy had become avail-

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able. This new drug had become the physician's favorite. The physician advised the patient to switch to this new drug, and the patient was eager to try it. Three weeks later, the patient came to see the physician to complain of continued malaise.

The patient may have been better served if he had undergone the following genetic tests, the results of which could have provided valuable management information:

- Test 1: A pre-dispositional test to determine whether the patient has a polymorphism associated with plaque development leading to coronary heart disease.
- Test 2: To see whether the patient has a polymorphism associated with a non-response to the medication (the newest medicine). A positive Test 2 indicates that the patient lacks an enzyme needed to metabolize the drug. The absence of the enzyme means that the drug is dispelled from the body without absorption.
- Test 3: To see whether the patient has a polymorphism which indicates the presence of an enzyme responsible for metabolizing the dosage too slowly, making the drug in that dosage toxic to the patient.
- The rational sequence of testing is 1-3.

If the patient tests negative, meaning that he does not have the polymorphism associated with plaque development, then his high cholesterol poses no health risk and medication to lower cholesterol levels are not indicated. If the patient tests positive, meaning that he does have the polymorphism, then he is predisposed to coronary heart disease (CAD) by virtue of being a plaque maker. In this case, cholesterol-lowering medication is indicated.

Ethical Issue #4: Whose right predominates?

The father of a research subject opened a letter addressed to his child and learned that his child had enrolled in a genetic research study.

- The letter indicated that for the purpose of research, the research facility had obtained some of the father's medical records. The father objected to what apparently was non-consensual disclosure of his medical information, even for the purpose of obtaining an informative family history to be used to provide optimal care for the son/daughter.
- Outraged, the father phoned the Office for Human Research Protections (OHRP)[5] of the U.S. Department of Health and Human Services, and protested that the researchers obtaining his family history without his explicit consent constituted a violation of his privacy rights. OHRP, siding with the father, blocked the offspring from using the father's information and forbade any further attempts to obtain more information on the grounds that an individual's right to privacy and autonomy is paramount.

Among the interesting and difficult issues in this case is the fact that it challenges us to think deeply about the weighted values we assign to first principles, namely the right to privacy. Whose right predominates in this case- the father's or the child's?

Federal medical privacy rules under the Health Insurance Portability and Accountability Act (HIPAA) spell out the requirements to ensure privacy of all individuals in the context of electronic health information transmission. Although several sectors of the health care industry opposed the adoption of these rules based on cost and impracticalities, HIPAA remains a barrier to unauthorized access of private health information. The Genetic Information Nondiscrimination Act (GINA), which passed in 2008, protects individuals, except those whose insurance is obtained through their small business employer and the uninsured, from substantial cost burdens based on their genetic profile. However, for numerous reasons, it is far from clear if and how these rules would support the father's claim.[4]

Ethical Issue #5: Could individuals be arguably coerced to undergo genetic testing in the context of the State's right to protect the public?

In knowing that the presence of an individual's gene variants can predict that certain drugs will not achieve the desired therapeutic benefit, it would not seem far-fetched to imagine that Medicaid and Medicare would not want to pay for drugs that do not work. Furthermore, those that result in greater cost burdens, such as hospitalization to treat adverse side effects. Particularly given state budget deficits, the cost incentive to test beneficiaries for drug response in advance of prescribing, if not also the desire to ensure positive patient outcomes, would seem compelling.

For example, roughly 5 percent of the population does not catalyze the conversion of codeine to morphine and thus achieve no pain relief. Knowing that non-codeine pain medication is indicated in advance of prescribing and realizing the failed efficacy is but one example of how considerable cost could be saved (perfectly good medi-

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cines would not be thrown away and costly adverse reactions would not occur). Whether the state would impose gene testing as a condition of enrollment or continued benefits is unclear, given the state's legal prerogative to enact legislation for the purpose of protecting its citizens.

Conclusion

In spite of our best efforts to anticipate and resolve ethical quandaries arising from the application of new genetic technologies, it is likely that unexpected conflicts will arise. Those discussed in this article are not intended as an exhaustive list.

The ethical issues here are remarkably similar to those standardly invoked in pre-dispositional testing discussions. Yet, arguably the stakes are lower here. The risk of psychological harm is, for the most part, far less substantial than testing for a late onset disorder like Huntington's disease for which effective treatment does not exist. Still, in the absence of guidance about what constitutes high and low stakes, ethically defensible decision-making requires acknowledgement of the competing interests and a broad enough scope of concern to analyze how an apparent low risk can become a high risk and vice versa.

Pharmacogenetics will permit gene profiling to answer questions about medicine responses, as well as enable researchers to design better and safer medicines. The science and its applications are real today and will be increasingly common in coming years. While the likelihood that individuals will be shut out from health insurance because they do not respond to a single drug or because a particular drug formula is toxic to them is extremely low, as would be employment exclusions (in hiring, promoting or job responsibilities), the issues underscore the importance of debating the ethical use of pharmacogenetics more widely.

In the United States, 45 million people lack any health insurance, and thus are at the mercy of hospitals' budgets for unrecoverable expenditures. Further, these individuals, and the many more millions of people with health insurance, have no access to sophisticated medical care due to limits imposed by insurers, especially for-profit managed care organizations and self-insured employers. Whether customized medicine will be available to all remains a large unknown. If history is a hint to how this new field will be used, we ought to act now to ensure that the benefits are available to all. ■

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