

PERSPECTIVES

OPINION

A call for the creation of personalized medicine databases

David Gurwitz, Jeantine E. Lunshof and Russ B. Altman

Abstract | The success of the Human Genome Project raised expectations that the knowledge gained would lead to improved insight into human health and disease, identification of new drug targets and, eventually, a breakthrough in healthcare management. However, the realization of these expectations has been hampered by the lack of essential data on genotype–drug–response phenotype associations. We therefore propose a follow-up to the Human Genome Project: forming global consortia devoted to archiving and analysing group and individual patient data on associations between genotypes and drug–response phenotypes. Here, we discuss the rationale for such personalized medicine databases, and the key practical and ethical issues that need to be addressed in their establishment.

There is an intricate interplay between hereditary, nutritional, environmental and lifestyle factors that affect the risk, severity and age of onset of complex disorders^{1,2}. Better insight into the genetic and epigenetic factors affecting complex disorders would greatly facilitate the implementation of personalized medicine that emphasizes the clinical use of individualized, genotype-based pharmacotherapy. Individual response to pharmacotherapy is determined by pharmacokinetic and pharmacodynamic factors that often depend on the individual's genotype^{2,3}. The factors governing drug efficacy for complex disorders such as asthma, diabetes and hypertension are myriad and unlikely to be deciphered from studies in small patient cohorts with hundreds of patients. Many studies of complex disorders report very small genetic effects for some gene alleles, and only rarely a large contribution to disease prevalence and severity by a single allele.

The intricacy of complex disorders, and the task of developing pharmacotherapy based on genotyping, expression analysis and/or proteomics profiling, is more challenging than some initially expected⁴. Indeed, some researchers have claimed that “reviews on this topic [pharmacogenomics] have painted an overly optimistic picture

— suggesting that the advent of individualized drug therapy used by the practicing physician is fast approaching”⁵. Others have taken the more positive view that the question is not if personalized medicine will arrive, but rather *when* it will arrive in the clinic⁶. It seems clear that the range of human genome diversity, combined with multiple non-heritable factors, creates a need for very large patient cohorts associated with high-quality data sets. Although improving drug safety using data from drug-metabolizing enzymes and transporter studies might be within reach, implementing drug individualization for optimal drug efficacy is significantly more challenging⁷.

Web-based biomedical databases

The Human Genome Project, funded by public resources and completed 2 years ahead of schedule in early 2003, was the most publicized and successful human consortium effort in biomedicine (see Further information). It has become a gauge by which future large international biomedical research projects will be measured. National science-granting authorities globally are looking for ways to follow this success, by promoting the formation of new collaborative efforts. Indeed, the recent European

Commission Sixth Framework Decision (10 June 2004) entitled ‘Integrating and Strengthening the European Research Area: Life Sciences, Genomics and Biotechnology for Health’ (see Further information) recommends and encourages the formation of consortia for genomics and biotechnology studies. Examples of well-known existing databases relevant to the intersection of genetics and pharmacology include DrugInteractions.com (see Further information) initiated by David Flockhart (Indiana University, USA), and the Human CYP Allele Nomenclature database by Magnus Ingelman-Sundberg (Karolinska Institute, Sweden) and others (see Further information). In the current Sixth Framework Program, a Network of Excellence has been launched, the European Model for Bioinformatics and Community Education (EMBRACE), which is a joint effort to make biological databases compatible (see Further information). A report on Human Genetic Research Databases by an expert working group of the Organisation for Economic Cooperation and Development (OECD) is expected to be published by the end of 2005 (see Further information). The recently established P3G Observatory (see Further information) is a web-based central repository for research tools facilitating the cooperation between biobanks and other population projects in genomics.

Developing web-based data resources might be the best way to stimulate the creation of a publicly accessible dataset for pharmacogenetics-based molecular medicine. The genomics era has illustrated the value of public sharing of data with the success of the National Center for Biotechnology Information (NCBI) at the National Institutes of Health (NIH), the Ensembl data resources at the European Bioinformatics Institute and many other resources worldwide. One particularly relevant precedent is the Pharmacogenomics and Pharmacogenetics Knowledge Base (PharmGKB; see Further information), which curates information relevant to pharmacogenomics, including genotypic variation, variation in drug-response phenotypes, drug-related metabolic pathways and curated literature^{8,9}. PharmGKB has a world-wide mission, but the majority of data

Box 1 | Key advantages of databases archiving PGx data from clinical trials

Advantages for the community

- Archiving data from clinical trials in open databases would make large datasets available for academic research
- Better insight about pharmacogenetics (PGx) would allow safer and more effective pharmacotherapy for complex disorders
- Collection of PGx data from many thousands of individuals, needed for understanding complex disorders, is beyond the capacity of public efforts, and would be facilitated by archiving data from clinical trials
- Improved knowledge on genetic risk factors for complex disorders would be constructive for early detection and treatment, which is crucial for age-related chronic disorders whose prevalence is rising due to 'graying' of industrialized nations
- Open data sharing combined with innovative bioinformatics tools would increase the power and reduce public spending for scientific research
- Data sharing from negative studies (also from academia) is of considerable benefit to the community, as knowledge is gained and human as well as financial investments in redundant studies can be avoided
- Data sharing would lead to emerging standards for measuring and exchanging common drug-response phenotypes

Advantages for the pharmaceutical industry

- Identification of better drug targets owing to improved knowledge from scientific studies
- More successful drug development process on genetically targeted patient populations
- Better public image: urgently needed in light of recent public outcry over poor drug safety and increasing drug prices
- Optional advantages from commercial and regulatory incentives would result in better revenues and less risk-taking in the drug development process
- Increased information on genetic factors related to adverse drug reactions would facilitate Phase IV post-marketing surveillance, contribute to drug safety, and reduce the risk of withdrawal from the market

submissions currently come from a relatively small set of investigators who are part of the NIH Pharmacogenetics Research Network (see Further information). Although current data archived by the PharmGKB includes drug-response phenotypes linked to some individual genotypes, the number of such linked observations is still rather small. Much of the data is on genotypic variation (not accompanied by clinical phenotypic data) for polymorphic gene alleles known to affect drug pharmacokinetics or pharmacodynamics. Ideally, datasets obtained from completed clinical trials should be archived in similar open-access databases. Archiving large sets of pharmacogenetic data collected and available at the level of individual patients will allow the use of web-based data searches and powerful computational tools. Unfortunately, efforts of the PharmGKB to include datasets from completed trials have so far been futile, reflecting the lack of motivation on the part of the pharmaceutical industry to contribute such data following the completion (or cancellation) of clinical trials.

A more specialized effort to encourage pharmacogenetic data sharing is the UCSF Pharmacogenetics of Membrane

Transporters (PMT) Project (see Further information), which currently curates specialized datasets about human membrane transporters. Notably, this database includes dedicated software for sharing pharmacogenetic datasets among research groups¹⁰.

The need for data sharing

A global consortium dedicated to data sharing in pharmacogenomics would facilitate the development of individual genotype-adjusted pharmacotherapy. In particular, there should be more active sharing of individual datasets of genotype and the corresponding drug-response phenotype data after publication of scientific manuscripts — a step that seems consistent with the current tendency towards transparency and harmonization in other fields as well¹¹. Presently, published manuscripts about pharmacogenetics might contain useful group data on genotype–drug-response phenotype correlates, but there is no means for sharing the individual datasets with other research groups, so that further analysis would become possible. There is, additionally, an unmet need for data sharing from unpublished studies, including unsuccessful clinical trials, cancelled trials and other studies that do not find their way into the main

body of scientific literature. Unless gathered in reliable and accessible public databases, such data typically remain the property of the pharmaceutical company that ran the trial, and contribute little to the research community. Moreover, the loss of this information constitutes a breach of the trust of the patients who contributed to the research through their consent for participation in clinical trials. The basic principles of modern research ethics, including those of reciprocity and universality, generate moral obligations between groups of people¹². Collecting samples and data for research from *individuals* gives rise to a duty for scientists to make the information available for the *collective benefit* of humankind. According to the principle of reciprocity, there is no contradiction here. The debate on data sharing has resurfaced, particularly in the European Union, in reaction to allegations that GlaxoSmithKline (GSK) was late to inform authorities of the danger of using paroxetine (Paxil) for adolescents¹¹. The withdrawal of rofecoxib (Vioxx; Merck) has similarly raised public concerns about the lack of data sharing by the pharmaceutical industry¹³. Among scientists, there is an increased interest in the urgent and yet unmet need for open-access, global, continuously updated and reliable databases dedicated to records of adverse drug reactions¹³.

One small but significant step in the direction of greater data sharing is the 2004 statement by the International Committee of Medical Journal Editors (ICMJE) calling for the establishment of a central registry of clinical trials¹⁴. This statement focused on the need to avoid bias in the publishing of data from negative or inconclusive clinical trials, as such bias significantly slows the development of medicine. A similar decision could be made by editors of leading biomedical and pharmacological journals, with regard to pharmacogenomics data from clinical trials. For example, it might be effective simply to require that data for clinical pharmacogenomics studies be deposited in a public database. An infrastructure is emerging to support the registration and tracking of clinical trials. Notable examples include the NIH Clinical Trials database ClinicalTrials.gov (see Further information) and the GSK Clinical Trial Register (see Further information). These elements, along with the large number of public genomic databases for genetic sequence data, microarray expression data, proteomics and 'boutique' gene family databases, provide a key step in disseminating knowledge about clinical studies from their inception through to the publication and submission

of datasets. The increased focus on phenotype in model organism databases, such as the Mouse Genome Informatics (MGI; see Further information), and at databases such as the PharmGKB, is the logical next step.

Ethical considerations

Ethical as well as legal considerations will play a major part in the creation of large databases for personalized medicine¹⁵. Researchers and the public have already begun to raise concerns about the ethical aspects underlying personalized medicine and patient privacy¹⁶, and these concerns, in particular about data collection and individual consent, could derail the realization of personalized medicine if not addressed carefully. There has been considerable concern about an apparent conflict between the pursuit of collective versus individual interests, in particular in the context of what among the general public is known as biobanking. However, the large-scale collection of genetic data is not in itself irreconcilable with individual benefit, as, for example, rare adverse effects will only become visible from very large datasets. Therefore, this type of data collection seems fully acceptable also from the classical bioethics perspective¹⁷. Moreover, new ethical frameworks increasingly take into account the developments in the area of science. Recent studies in bioethics focus on, for example, the concept of genetic equity¹⁸, and on the emerging shift in emphasis towards a community-oriented research ethics¹² without replacing individual human dignity as a core value. But it should be recognized that no ready-made, general solutions are available for the most burning issues, such as the consent for future, as yet undefined, use of data and samples, and the implications of anonymization.

Routes for moving forward

The development of frameworks for data sharing is not without major obstacles that require innovative solutions. Much information is commercial and an appropriate balance must be sought to ensure that competition and innovation are not stymied by public efforts to archive drug trials data. On the contrary, incentives should be devised so that sharing of data is encouraged and rewarded. There are several mechanisms that could be considered for promoting the willingness of the private sector to deposit data from completed (or aborted) clinical trials. In the real-world, for-profit setting of pharmaceutical companies, such incentives must be based on economic rather than altruistic concerns. The incentives could include, for

example, tax exemptions for costs of collecting the genomics and proteomics data that are later deposited in public databases. A second route might include incentives of speeding up the drug application evaluation process when the relevant clinical and genomic datasets are deposited in a dedicated public database, along with a mechanism ensuring that data remain outside the public domain prior to the final drug approval. A third route for incentives could include legislation favouring lengthened patent lives for drugs whose entire clinical trials datasets are deposited in such public databases. The latter route would certainly require a major revision in the drug-application process and international patent legislation. In light of the apparent need for a major reorganization of the drug development process at large, the time seems ripe to explore such incentives with a lively public debate^{19–21}.

A public consortium for personalized medicine will require community supervision, administration and funding to ensure the highest data quality. Based on the experience of the PharmGKB, we can estimate that an initial investment in the range of US\$50–100 million over a period of 5–10 years would potentially allow the project to begin. Larger investments might be required if the databases become successful and accumulate datasets from a large number of clinical trials.

“ The time has come to gather the accumulated pharmacogenetic data, knowledge and expertise for the benefit of the community. ”

The need for reciprocity between the pharmaceutical business and the community has been an intensely debated issue^{22,23}. Discussion has traditionally focused on the incapacity of developing countries to afford costs of new drugs. However, given the escalating costs of pharmacotherapy for national health budgets in industrialized nations, the issue of benefit sharing now seems a global concern. So, in the context of improving drug safety and efficacy with pharmacogenomics knowledge, having a lead role in setting-up and funding personalized medicine consortia could be an appropriate way for the pharmaceutical industry to reflect the need for reciprocity. Such support could be envisaged along the lines of the model of the SNP Consortium, which enjoyed support from the private sector for

Box 2 | Data sharing: ethical considerations

- Reciprocity, universality and solidarity call for data sharing: individual donations to research (through trial participation) should be available for the benefit of all
- Ownership of genomic information: individual property or common heritage?
- Public trust builds on transparency: publication of any available study outcome is a moral and social requirement
- The price of the quid pro quo: reciprocity, how much is it worth?
- Effectuating data sharing — what means are needed and what can be justified: coercion, incentives, or the appeal to moral duties and social responsibility?

cataloguing human SNPs in a public database (see Further information). However, it is likely that public funding would also be required, and we call upon policymakers to consider the long-term benefits for society from such investments. This is one of the issues currently being studied by the Pharmacogenetics Working Group of the OECD. Notably, costs for establishing and running open ‘personalized medicine’ databases are likely to represent a small fraction of the US\$3 billion of public funds put into the Human Genome Project. It would be regrettable if the improvements in human health promised by this project were not realized because of a failure to implement appropriate pharmacogenomic data-collection schemes.

The investment could pay off for society within about 20 years — in reduced healthcare costs due, in part, to a reduction in the frequency of adverse drug reactions (ADRs). In the United States alone, ADRs are estimated to cost society ~US\$10 billion annually²⁴ and total US annual health expenditures related to lack of drug efficacy have been estimated at the staggering figure of US\$170 billion²⁵, which is larger than the total amount spent on prescription drugs in the United States. Moreover, ADRs were estimated to account for the equally staggering figure of about 6.5% of new hospital admissions^{26,27}. In addition to ADRs, pharmacogenomics also attempts to improve the efficacy of pharmacotherapy, further contributing to a potential reduction of healthcare costs worldwide.

Pharmacogenomic information collected in clinical trials and deposited in personalized medicine databases should be organized using standardized terminologies and phenotype descriptors. The complex task of accurately recording phenotypes will require

the use (and extension) of terminology systems such as the Unified Medical Language System²⁸ and its contributing vocabularies. This could include the HL7 Clinical Document Architecture, Release 2 (REF. 29), the SNOMED system for describing symptoms and diseases³⁰, the LOINC system for transferring information about laboratory tests³¹, and improved systems for accurately classifying and describing drug-response phenotypes, such as those adopted by the Mouse Genome Initiatives³². The significance of creating a robust infrastructure for classifying and describing phenotypes is that it would maximize the opportunity to integrate data from different trials, standardize the collection (and exchange) of commonly measured phenotypes, and allow search and analysis of related drug-response phenotypes over the complete range of datasets brought together as part of an effort to standardize diagnostic criteria and methods for describing clinical outcomes.

The creation and continuous updating of the proposed databases would hopefully be possible with direct participation of the private sector along with publicly funded efforts³³. Some key issues concerning the setting up of open personalized medicine databases and related ethical questions are summarized in BOXES 1, 2.

Conclusions: turning data into insights

Web-based bioinformatics tools have become powerful resources for genomics studies. The power of such tools is most notable when very large datasets need to be collaboratively analysed to find subtle genotype-phenotype associations encountered in the study of complex disorders. This potential, the information from the completed Human Genome Project, and the valuable pharmacogenetic datasets collected during clinical trials must be harnessed to implement the vision of personalized medicine in the form of genotype-based pharmacotherapy. We fully agree with the statement by van Ommen that "well-accessible resources are a prerequisite for turning data into insights"³⁴, and open data sharing is the best instrument for building such resources.

Pharmacogenetics is not a new discipline: it is almost 50 years old, and the time has come to gather the accumulated pharmacogenetic data, knowledge and expertise for the benefit of the community. This endeavour will primarily require the collaboration of the pharmaceutical industry, which might require appropriate regulatory and financial incentives. It would also require generous public

funding, as well as innovative international agreements favouring sharing and publishing of pharmacogenetic data by both the public and the private sector. The investment is likely to pay off with safer and more effective medicines, allowing reduced human suffering, smaller overall healthcare costs and improved community health. An infrastructure to support personalized medicine could be the best pay-off for the public investment in the Human Genome Project.

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Competing interests statement

The authors declare no competing financial interests.

FURTHER INFORMATION

Human Genome Project: http://www.ornl.gov/sci/techresources/Human_Genome/project/about.shtml
 ClinicalTrials.gov: <http://www.clinicaltrials.gov>
 DrugInteractions.com: <http://www.drug-interactions.com>
 EMBRACE Network of Excellence: <http://www.embracegrid.info>
 European Commission Sixth Framework Decision: Integrating and Strengthening the European Research Area: Life Sciences, Genomics and Biotechnology for Health: <http://www.mrc.ac.uk/pdf-WorkProgTP1-call3.pdf>
 GlaxoSmithKline Clinical Trial Register: <http://ctr.gsk.co.uk/welcome.asp>
 Human Cytochrome P450 Allele Nomenclature Committee: <http://www.imm.ki.se/CYPalleles/>
 Mouse Genome Informatics: <http://www.informatics.jax.org>
 NIH Pharmacogenetics Research Network: <http://www.nigms.nih.gov/pharmacogenetics>
 Organisation for Economic Co-operation and Development: <http://www.oecd.org>
 P3G Observatory: <http://www.p3gobservatory.org>
 PharmaGKB: <http://www.pharmgkb.org>
 The SNP Consortium: <http://snp.csh.org/>
 UCSF Pharmacogenetics of Membrane Transporters: <http://pharmacogenetics.ucsf.edu/>
 Access to this interactive links box is free online.

Links

ClinicalTrials.gov: <http://www.clinicaltrials.gov>

DrugInteractions.com: <http://www.drug-interactions.com>

EMBRACE Network Of Excellence: <http://www.embracegrid.info>

European Commission Sixth Framework Decision: Integrating and Strengthening the European Research Area: Life Sciences, Genomics and Biotechnology for Health:
<http://www.mrc.ac.uk/pdf-WorkProgTP1-call3.pdf>

GlaxoSmithKline Clinical Trial Register:
<http://ctr.gsk.co.uk/disclaimer.asp>

Human Cytochrome P450 Allele Nomenclature Committee:
<http://www.imm.ki.se/CYPalleles/>

Mouse Genome Informatics: <http://www.informatics.jax.org>

NIH Pharmacogenetics Research Network:
<http://www.nigms.nih.gov/pharmacogenetics>

Organisation for Economic Co-operation and Development:
<http://www.oecd.org>

P3G Observatory: <http://www.p3gobservatory.org>

PharmaGKB: <http://www.pharmgkb.org>

The SNP Consortium: <http://snp.cshl.org/>

UCSF Pharmacogenetics of Membrane Transporters:
<http://pharmacogenetics.ucsf.edu/>

Biographies

David Gurwitz received his Ph.D. from the Department of Biochemistry at Tel-Aviv University in 1986 and in 1989 completed his postgraduate studies at the University of California Irvine. He then joined the Israel Institute for Biological Research, where he headed the biochemistry team in a project developing M1-selective muscarinic agonists as Alzheimer's disease therapeutics. The leading compound AF102B (Cevimeline) received FDA approval for Sjogren's syndrome. Since 1995, he has directed the National Laboratory for the Genetics of Israeli Populations at the Department of Human Genetics and Molecular Medicine in Tel-Aviv University. David's current research interests include pharmacogenetics, which he teaches to M.D. and graduate students. He has co-authored over one hundred scholarly publications and is a member of several editorial boards. He currently represents the Israel Ministry of Science and Technology at the OECD Steering Committee on Pharmacogenetics.

Jeantine Lunshof is a philosopher engaged in bioethics. She studied philosophy and Oriental linguistics in Hamburg, and philosophy (ethics; medical ethics) and health law in Amsterdam (UvA). She carried out several projects concerned with ethical aspects of human genetics at the universities of Bamberg, Heidelberg and Düsseldorf, and was also engaged in EU projects in the Biomed I and II, and in the Biotech-programme. She worked for the Berlin-Brandenburg

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Russ Altman is Professor of Genetics, Bioengineering and Medicine (and of computer science by courtesy) at Stanford University. His primary research interests are in the application of computing technology to basic molecular biological problems of relevance to medicine. He is currently developing techniques for collaborative scientific computation over the Internet, including novel user interfaces to biological data, particularly for pharmacogenomics (for example, <http://www.pharmgkb.org/>). Other work focuses on the analysis of functional microenvironments within macromolecules and the application of algorithms for determining the structure, dynamics and function of biological macromolecules (for example, <http://simbios.stanford.edu/>). Dr. Altman holds an M.D. from Stanford Medical School, a Ph.D. in medical information sciences from Stanford, and an A.B. from Harvard College. He has been the recipient of the U.S. Presidential Early Career Award for Scientists and Engineers, a National Science Foundation CAREER Award. He is a fellow of the American College of Physicians and the American College of Medical Informatics. He is a past-president and founding board member of the International Society for Computational Biology, an organizer of the annual Pacific Symposium on Biocomputing. He currently directs the Stanford Center for Biomedical Computation, and he won the Stanford Medical School graduate teaching award in 2000.

TOC blurb

Gurwitz and colleagues propose that consortia dedicated to archiving and analysing data on associations between genotypes and drug-response phenotypes could allow the potential of personalized medicine to be realized, and discuss the associated practical and ethical issues that need to be addressed.