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Pharmacogenomics: will the promise be fulfilled?

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Abstract

Tools such as genome resequencing and genome-wide association studies have recently been used to uncover a number of variants that affect drug toxicity and efficacy, as well as potential drug targets. But how much closer are we to incorporating pharmacogenomics into routine clinical practice? Five experts discuss how far we have come, and highlight the technological, informatics, educational and practical obstacles that stand in the way of realizing genome-driven medicine.

Which have been the most exciting or unexpected recent developments in pharmacogenomics?

Russ B. Altman. I think there have been surprises in two areas. First, there are the recent reports of individualized therapy of cancers based on the deep resequencing of cancer genomes, and the discovery of mutated proteins that could be targeted with drugs that are not normally used for these types of cancers. One example is the treatment of tongue cancer with RET inhibitors[1]; here, knowledge of the genetic defects that are present in the cancer allowed drugs to be selected on the basis of their molecular mechanisms, in an individualized manner. This work underscores the potential ability to use genome information to make focused treatment decisions. Second, in the course of annotating a complete genome sequence for variants that affect drug response[2], we were surprised to discover that potentially useful information could be obtained about the link between genetic variants and drug response for hundreds of drugs. Even though many of these links were

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made at low confidence, they could be useful in clinical conditions for which several drugs might be suitable. In these situations, the suggestion of a differential benefit–harm relationship based on genetic data could tip the clinical decision. Some of the links were established at high confidence, and these have a much clearer value for present-day application.

Heyo K. Kroemer. One exciting but expected advance in the field of pharmacogenomics is the clinical verification of genetically determined 'high-risk pharmacokinetics'. This term was coined to describe a drug that relies on a single pathway for either bioactivation or inactivation[3]. If loss-of-function variants are present in the population, large variations in drug effects are predicted[4]. The most exciting clinical example of high-risk pharmacokinetics is the unfolding story of tamoxifen, a drug used in oestrogen-receptor-positive breast cancer. Tamoxifen requires bioactivation by CYP2D6 (a cytochrome P450 isoform), which is present at reduced levels in 7% of Caucasian women. In fact, recent data indicate that there is an association between the presence of functional CYP2D6 variants and the clinical outcome of breast cancer[5]. In addition to its clinical consequences (testing for functional CYP2D6 alleles before therapy is currently being considered by the US Food and Drug Administration (FDA)), this discovery has potential pharmacoeconomical relevance: if treatment with tamoxifen were restricted to women with functional CYP2D6 variants, the proven clinical superiority of aromatase inhibitors over tamoxifen might be questioned.

Another exciting and unexpected finding is the identification, using genome-wide association (GWA) studies, of lumiracoxibinduced liver injury in individuals with distinct human leukocyte antigen (HLA) alleles[6]. In this situation, the exclusion of patients that are at risk for this particular lumiracoxib side effect may lead to the resuscitation of a deceased drug.

Catherine A. McCarty. I can't point to any one specific discovery in elucidated causal mechanisms. Instead, I think that the exciting developments in pharmacogenomics lie in the laboratory and analytical tools that are being developed at amazing speed. Reliable ADME chips (which assay absorption, distribution, metabolism and excretion) are now available commercially to facilitate pharmacogenetic discoveries, and the cost of carrying out GWA studies and sequencing is dropping dramatically, providing data for discovery at an unprecedented rate.

Mark J. Ratain. The most exciting recent development in pharmacogenomics is the outcome of the first genome-wide pharmacogenomic studies. A number of such studies have identified variants of significant clinical importance in the context of predicting both efficacy and toxicity. Although some of these studies have identified known functional polymorphisms in genes that might have been obvious candidates (in hindsight), most have identified variants that would not have been considered in a candidate gene approach.

Dan Roden. We have seen dramatic increases in our understanding of the mechanisms of drug action and of the genetic determinants of variable responses to old and widely used drugs, such as warfarin[7], tamoxifen[5] and clopidogrel[8].

The GWA study approach has been applied to identify genetic contributions to variable drug responses and, interestingly, has often identified loci that are not novel but rather that act in pathways that are obvious pharmacokinetic or pharmacodynamic candidates[9–12]. To me this result indicates that, in pharmacogenomics, single variants can exert relatively large effects on variable drug outcomes — a finding that has implications for clinical implementation. As with other GWA studies[13], a large portion of variability remains unexplained after GWA 'hits' and clinical covariates have been analysed. That means that single common variants

explain only part of variable drug responses, and we have to look elsewhere for the rest; the next frontiers for pharmacogenomics will be to analyse rare variation, and pathway and gene–gene interaction effects.

A third exciting result has occurred in cancer genomics. We now have an increasing catalogue of specific mutations that drive cancer in individual patients, and we are learning that targeting the cancer genomic profile that is specific to an individual patient can yield unprecedented cure rates[14,15].

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Heyo K. Kroemer, Ph.D., has been Professor and Chairman in the Department of Pharmacology since 1998, and from 2000 has been the Dean of the School of Medicine at Ernst Moritz Arndt University in Greifswald, Germany. He received his postdoctoral training in clinical pharmacology at Vanderbilt University in Nashville, Tennessee, USA, and later at the Dr Margarete Fischer Bosch Institute of Clinical Pharmacology in Stuttgart, Germany. His research is focused on the contribution of drug transport to variable drug response in humans. Since 2009, he has been the principal investigator of the GANI_MED (Greifswald Approach to Individualized Medicine) consortium, an international group involved in translating personalized medicine into the clinical setting.

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Dan Roden is a clinician–scientist who is Professor of Medicine and Pharmacology and Assistant Vice-Chancellor for Personalized Medicine at Vanderbilt University School of Medicine. His research career has focused on pharmacogenomics, with a particular emphasis on cardiac arrhythmias. He is the principal investigator for the Vanderbilt sites of the US National Institutes of Health's Pharmacogenomics Research Network (where he currently serves as chair of the steering committee) and the Electronic Medical Records and Genomics Network of the National Human Genome Research Institute. He directs BioVU, the Vanderbilt DNA databank that currently links DNA samples from more than 100,000 patients to de-identified electronic medical records.

Is personalized medicine attainable, and which factors affect its adoption?

R.B.A. I think the factors that affect adoption are clear. First, we need to educate physicians in the proper use of genetic information. In particular, physicians need to be made aware of the limits and potential of using genetic information to adjust probabilities. Physicians routinely make similar considerations with other tests, but they have not always applied the same framework to drug prescription. I am involved in a consortium that is writing suggested guidelines for pharmacogenetics clinical practice, to give early adopters some specific guidance. Second, we need to create electronic medical record (EMR) systems that will 'pop up' pharmacogenetic information at the appropriate time during a prescribing decision, so that (similar to drug interaction warnings) physicians can be alerted to opportunities to modify their prescribing at the right moment. Third, and perhaps most importantly, we need to oppose the idea that every pharmacogenetic intervention requires a randomized controlled trial (RCT) to prove its superiority over the existing standard of care. Of course, there should be evidence of efficacy, but the level of evidence needs to match the clinical stakes. RCTs should be reserved for high-stakes prescribing decisions (involving lots of risk to the patient (as in the case of cancer) and/or many patients (as in the case of anticoagulation therapy)). Other levels of evidence may be sufficient to justify the preliminary testing of pharmacogenetics in clinical settings. Finally, we must carefully monitor the effect of pharmacogenetic interventions — as we should for all interventions — to evaluate the degree of data that are sufficient to establish benefit (or lack of benefit) of specific interventions.

H.K.K. Currently, we do not know whether personalized medicine is attainable. The idea that 'the right treatment for the right patient at the right time' leads to decreased side effects and costs remains to be proven on a larger scale. However, the tools to answer this question are becoming increasingly available.

I think that the battle around personalized medicine will be won or lost with the availability of reliable phenotypes. In particular, the accuracy of phenotyping in clinical practice is rather limited, even for simple measures (for example, blood pressure or weight) and so phenotypic associations between clinical traits and genomic data might be missed. Progress in the field of genomics has been rapid (for example, through the use of GWA studies) and will become more powerful when it is combined with reliable phenotypes. The development of personalized medicine-related bioinformatics and hospital informatics (a grossly underestimated field) will contribute greatly to the successful adoption of personalized medicine. A wealth of ethical considerations must also be met in a prospective manner; these issues range from ensuring appropriate informed consent and data safety to establishing a new type of physician–patient relationship. The implementation of

personalized medicine in a health care setting is of paramount importance. Taken together, we now have the tools and we need to develop appropriate trials to answer this question.

C.A.M. Personalized medicine is very definitely attainable. Three factors affect its adoption. First, it is necessary to make and validate discoveries, and to determine whether genetic-based prescribing is both effective and cost-effective. After discoveries have been made and validated, the two major factors that affect translation of personalized medicine are the acceptance of a thirdparty payer system (that is, the financing of personal health services by an organization other than the patient or the health care provider) and patient coverage by EMRs. As with any new diagnostic test, third-party payers in the USA require approval by the FDA and evidence of cost-effectiveness when making coverage decisions. A Progress Report on Electronic Health Records in US Hospitals from the Robert Wood Johnson Foundation revealed that there were basic or comprehensive EMRs in only 11.9% of US hospitals in 2009.

M.J.R. Personalized medicine is definitely attainable, although it is not yet possible to determine the full impact of this approach, as there is never a perfect correlation between genotype and phenotype. However, it is unlikely that we will make major advances if we continue to view a patient's genotype data as a laboratory test, as this necessitates a laboratory order, a delay until the result is available, a cost per unit test and results in an uncertain reimbursement. Instead, we need to consider the genetic exam as a separate component, more akin to medical history and physical examination. In this context, genetic information would be available to the physician at the time of the encounter with the patient and could be used in real time. However, this will require significant investments in information technology and education to assist physicians in the interpretation of such information, as well as a means to cover the relatively modest costs of acquiring medically useful genotype information.

D.R. I will first say that personalized medicine encompasses not only genomics but also many other factors such as personal and cultural preferences. I am optimistic that we can achieve a health care vision that incorporates these considerations and pharmacogenomics into practice. Three key components will be required to realize this vision. First, we need inexpensive and reliable genotyping, and we are getting close to that. Second, we should develop robust EMR systems that not only archive individual patient data but can aggregate data and can deliver 'point-of-care' decision support; there is simply too much information for any busy practitioner to remember, let alone to decide how best to respond to variant genotypes. In addition, as we place genomic information into EMRs, they will also become an engine for discovery. And third, we must develop a consensus around what constitutes 'actionable' genotypes; these may be individual variants or collections of variants whose implications we are only now beginning to explore. There will also be other needs, such as educating health care providers and the public, and making the economic case for personalized medicine.

What are the challenges to ensuring full and fair access to the results of pharmacogenomics research and their appropriate use?

R.B.A. One big fear is that information about allele frequencies in different ethnic populations will lead to the differential development of drugs for alleles associated with more wealthy populations. I don't think we have examples of that at this time, but it is not an unreasonable concern.

I think that, to the extent that academic medical centres are the first to roll out pharmacogenomics (for example, the laudable efforts in this area by researchers at

Vanderbilt University), and to the extent that these academic centres often help to serve patients from lower socioeconomic backgrounds, the fruits of pharmacogenomics may come to these populations more quickly. In addition, I am aware of several efforts in pharmacogenomics that focus on traditionally under-served populations (for example, Native Americans, who are the subject of a study led by Ken Thummel at the University of Washington in Seattle, and African Americans, who are studied as part of our work in the International Warfarin Pharmacogenetics Consortium). I therefore think that the research community has appropriately targeted important pharmacogenetic questions for these populations.

Finally, I think that the Genetic Information Nondiscrimination Act (GINA) of 2009 was a good first step in deploying general protections for individuals to prevent discrimination on the basis of genetics.

H.K.K. Pharmacogenomics has, beyond any doubt, contributed to our understanding of the mechanisms of interpatient variability in drug response. The translation of such knowledge into the clinic, however, has been restricted to few examples. Therefore, clinical research in pharmacogenomics needs to be restructured in large international consortia to ensure timely results. For example, clinical trials aimed at testing the relevance of adjusting the dose of the anticoagulant warfarin according to genotype[16] may take so much time that, by the time the results are available, warfarin will have been replaced by new compounds.

Analytical methods used in pharmacogenomics should be reliable and affordable. Technologies with the potential of providing information additional to genotypes at reasonable costs (for example, metabolomics) have to be screened for their potential contribution.

Last, but most important, both patients and physicians need to be informed about the add-on value of pharmacogenomics for the outcome and safety of drug therapy.

C.A.M. First and foremost, studies need to be conducted in all racial or ethnic groups. This has been a challenge because racial or ethnic minorities are under-represented in most biobanks in the United States. However, provided a causal marker is polymorphic in a given population, the relative association between a variant and disease risk is likely to be the same across racial or ethnic groups[17]. More data are needed to document racial and ethnic variation in allele frequencies, as well as the association between markers and drug efficacy and adverse drug reactions. Full and fair access to genetic-based prescribing when it becomes ‘standard of care’ raises the same issues of health equity that exist for all health services, and equal access does not necessarily lead to equal use[18].

M.J.R. The results of pharmacogenomics research should eventually be applicable to all patients who are candidates for medication, although it is likely that there will be a delay between the first clinical applications and widespread use. Currently, a number of companies offer genotyping directly to patients, and many patients are willing to pay for such information themselves, regardless of the utility to their physicians. One significant challenge is to distinguish between genotypic data that are primarily useful for predicting disease risk and those that are focused on disease treatment. Variants that identify an increased genetic risk of a serious disease can inform patients and physicians regarding interventions to diminish the environmental risk of such disease. However, this information should not be used for financial purposes, which would include employers and insurance carriers, as well as patients. The optimal legal context for managing such information will require further study, as it is unfair (and in some regard illegal) for insurance companies to discriminate against patients, but it is also unfair (and in some regard illegal) for patients to

purchase some insurance policies (for example, life insurance) without disclosing such increased risk to the insurance company.

D.R. At the most generic level, good science and scientific advances rely on public dissemination and discourse of the results of experiments. This applies to a broad range of scientific inquiry, and pharmacogenomics is no exception; in addition, as in many areas in genome science, big numbers are required to give precision and confidence to the results. It is self-evident that every large clinical trial of a new or old drug yields variable outcomes. Accordingly, I think that those who design and manage large and expensive clinical trials must anticipate the need to examine genetic and many other factors that may have an impact on response to promising therapies.

What do you expect the field to achieve in the next 5 years?

R.B.A. First, I hope that we will begin to see early-adopter health care delivery systems roll out pharmacogenetics testing, and begin to report on the differences in outcome that they observe. The large amount of interest that currently exists in comparative effectiveness research should help here: we should introduce interventions for which there is an adequate level of evidence, and we should then watch and learn formally whether the interventions are paying off. This work should be done in health care systems that have excellent EMRs, so that access to the outcomes is routine and comprehensive.

Second, I think we will see an increased ability to interpret the functional impact of rare variants that are being discovered by whole-genome sequencing. This is crucial, because rare variants may underlie important phenotypes, and so we will need new ways to infer their likely effects, both computationally and experimentally.

Finally, I hope that pharmacogenetics will start feeding back on the drug discovery and drug development process and maybe begin to show a path towards a more efficient system of delivering new drugs to the public. This is a long-term goal, but I think that pharmacogenetic thinking may be valuable in this context because of its focus on molecular mechanisms, gene–drug interactions and systems approaches to understanding how sets of genes combine to affect drug response.

H.K.K. In general, I expect that pharmacogenomics will redefine its role and integrate itself in the larger framework of personalized medicine[19]. It will be increasingly clear that the contribution of pharmacogenomics to treatment outcome will vary substantially between compounds. The above picture of high-risk pharmacokinetics will not be the standard situation in drug therapy.

The integration process of pharmacogenomics into personalized medicine will be driven by the new technologies available, ranging from improved phenotyping, GWA studies, deep sequencing and metabolomics to imaging technologies. Using contemporary bioinformatics, the field will move away from the idea that a single gene (or, at most, its haplotypes) governs drug response in the setting of complex and chronic diseases. The application of such approaches should have major consequences for drug development and for the design of clinical trials.

C.A.M. I expect many more discoveries to be made in the next 5 years to identify genetic predictors of response to medications, in terms of both efficacy and adverse reactions. Large-scale biobanks that are linked to EMRs will continue to provide source material for timely discoveries, particularly related to efficacy[20]. I expect additional large collaborations, such as the International Serious Adverse Events Consortium, to identify genetic predictors

of rare adverse events. I expect to see increased black box label warnings from the FDA. I expect to see genetic testing incorporated into point-of-care decision tools for physicians.

M.J.R. A number of feasibility studies of personalized medicine are ongoing, some of which are aimed at modifying disease risk and some of which are focused on modifying physician prescribing. These feasibility studies have the common feature of anticipatory genotyping (that is, genotyping before the development of a specific clinical indication). Over the next 5 years, many of these studies will have been completed, hopefully paving the way for widespread use of personalized medicine.

D.R. We will continue to use basic and translational science to understand why drug responses vary among patients — this has been the pathway to progress in the discipline of clinical pharmacology and pharmacogenomics. The convergence of genome science with information science and EMR systems will allow us to start to deploy this information in a contemporary, point-of-care decision support environment.

We must rethink the old paradigm of ordering a drug, recognizing the evidence that genomic variants may have a role in determining response to that drug, ordering a genetic test, waiting for the result and adjusting the dose accordingly. At our own institution, we have taken the first steps in implementing a 'pre-prescription genotyping' [21,22] paradigm: we are now identifying patients who are likely to receive drugs that have a compelling pharmacogenomic 'story' and embedding genetic information in those patients' charts before drug prescription. We feel that this approach will allow us to begin to understand in detail the issues involved in widespread uptake: what action do we take in the face of variant genotypes? How do we make the economic case for genome-driven medicine? How do patients and health care providers respond?

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