6. Food and Drug Administration. *FDA Approves restricted marketing of Lotronex*. <http://www.fda.gov/bbs/topics/NEWS/2002/NEW00814.html> (Department of Health and Human Services, Washington, 2002).
7. Houn, F. Letter, NDA-21-107/S-005, Office of Drug Evaluation II, Centre for Drug Evaluation and Research <http://www.fda.gov/cder/foi/appletter/2002/21107s5ltr.pdf> (Food and Drug Administration to GlaxoSmithKline, 2002).
8. Goldstein, D. B. Pharmacogenetics in the laboratory and the clinic. *N. Engl. J. Med.* **348**, 553–556 (2003).
9. Holtzman, N. A. in *Pharmacogenomics: Social, Ethical, and Clinical Dimensions* (ed. Rothstein, M. A.) 163–186 (Wiley-Liss, Hoboken, New Jersey, 2003).
10. Omenn, G. & Motulsky, A. in *Pharmacogenomics: Social, Ethical, and Clinical Dimensions* (ed. Rothstein, M. A.) 137–162 (Wiley-Liss, Hoboken, New Jersey, 2003).
11. Nuffield Council of Bioethics. *Pharmacogenetics: Ethical Issues* (Nuffield Council of Bioethics, London, 2003).
12. Melzer, D. *et al. My Very Own Medicine: What Must I Know?* <http://www.phpc.cam.ac.uk/epg/Report.pdf> (Department of Public Health and Primary Care, Univ. Cambridge, Cambridge, 2003).
13. Lindpaintner, K. Pharmacogenetics and the future of medical practice. *Br. J. Clin. Pharmacol.* **54**, 221–230 (2002).
14. Pirmohamed, M. & Park, B. K. Genetic susceptibility to adverse drug reactions. *Trends Pharmacol. Sci.* **22**, 298–305 (2001).
15. Roses, A. Pharmacogenetics and the practice of medicine *Nature*, **405**, 857–865 (2000).
16. Clozapine Summary Sheet SS95/09 <www.keele.ac.uk/depts/mm/MTRAC/ProductInfo/summaries/C/CLOZAPINEs.html> (MTRAC, Department of Medicines Management, Keele Univ, Keele, 1995)
17. Arranz, M. J. *et al.* Pharmacogenetic prediction of clozapine response. *Lancet* **355**, 1615–1616 (2000).
18. Mancama, D., Arranz, M. J. & Kerwin, R. W. Genetic predictors of therapeutic response to clozapine: current status of research. *CNS Drugs* **16**, 317–324 (2002).
19. Holtzman, N. A. & Watson, M. S. (eds) *Promoting Safe and Effective Genetic Testing in the United States*. Final Report. (Johns Hopkins Univ. Press, Baltimore, Maryland, 1998).
20. Robertson, J. A., Brody, B., Buchannan, A., Kahn, J. & McPherson, E. Pharmacogenetic challenges for the health care system. *Health Aff.* **21**, 155–167 (2002).
21. Rothstein, M. A. & Epps, P. G. Ethical and legal implications of pharmacogenomics. *Nature Rev. Genet.* **2**, 228–231 (2001).
22. Issa, A. M. Ethical perspectives on pharmacogenomic profiling in the drug development process. *Nature Rev. Drug Discov.* **1**, 300–308 (2002).
23. Smart, A., Parker, M. & Martin, P. Tailored medicine: who will it fit? The ethics of patient and disease stratification. *Bioethics* (in the press).
24. Pirmohamed, M & Lewis, G. in *Regulating Pharmaceuticals in Europe: Striving For Efficiency, Equity and Quality* (eds Mossialos, E., Mrazek, M. & Walley, T.) 279–296 (Open Univer. Press, Maidenhead, 2004).
25. Stearns, V., Davidson, N. E. & Flockhart, D. Pharmacogenetics in the treatment of breast cancer. *Pharmacogenetics* **4**, 143–153 (2004).
26. Marsh, S. & McLeod, H. Cancer pharmacogenetics. *Brit. J. Cancer* **90**, 8–11 (2004).
27. Department of Health and Human Services. Draft guidance for industry: pharmacogenomic data submissions <http://www.fda.gov/OHRMS/DOCKETS/98fr/03d-0497-nad0001vol1.pdf> (Food and Drug Administration, 2003).
28. Savage, D. R. FDA guidance on pharmacogenomics data submission. *Nature Rev. Drug Discov.* **2**, 937–938 (2003).
29. The European Agency for the Evaluation of Medicinal Products. Concept paper on pharmacogenetics — briefing matters. CPMP/4445/03 <http://www.emea.eu.int/pdfs/human/pharmacogenetics/444503en.pdf> (The European Agency for the Evaluation of Medicinal Products, 23 Jan 2003).
30. Lesko, L. J. & Woodcock, J. Pharmacogenomic-guided drug development: regulatory perspective. *Pharmacogenomics J.* **2**, 20–24 (2002).
31. Ratner, M. L. Pharmacogenomic data and labeling: a less-safe harbor for existing drugs? *Windhover's Update* <http://www/windhover.com/update/05252003/2003800094> (2003).
32. Anonymous. FDA's Lesko says pharmacogenomics guidance paper due mid-year. *Pharmacogenomics Reporter (New York)* 6 (17 Jan 2003).
33. Abraham, J. & Lewis, G. *Regulating Medicines in Europe* (Routledge, London, 2000).
34. European Commission. The *in vitro* diagnostic medical devices directive (98/79/EC). *Official J. Eur. Communities* L331/1 (27 Oct 1998).
35. Danzon, P. & Towse, A. The economics of gene therapy and of pharmacogenetics. *Value Health* **5**, 5–13 (2002).
36. Audit Commission. A spoonful of medicine: medicines management in NHS hospitals. <http://www.audit-commission.gov.uk/Products/NATIONAL-REPORT/E83C8921-6CEA-4b2c-83E7-F80954A80F85/nrspoonfulsugar.pdf> (Audit Commission, London, 2001).

Acknowledgements

This research on which this paper is based was supported by a Wellcome Trust grant titled 'The clinical and commercial development of Pharmacogenetics'.

Competing interests statement

The authors declare no competing financial interests.

Online links

FURTHER INFORMATION

Encyclopedia of Life Sciences: http://www.els.net/pharmacogenetics
Institute for the Study of Genetics, Biorisks and Society: http://www.nottingham.ac.uk/igbis
Lewis' homepage: http://www.york.ac.uk/org/satsu/Staff/graham/graham.htm
Oxford Genetics Knowledge Park: http://www.oxfordgkp.org
Pharmacogenetics research at SATSU: http://www.york.ac.uk/res/pgx
University of York Science and Technology Studies Unit: www.york.ac.uk/org/satsu
Webster's homepage: http://www.york.ac.uk/depts/soci/s_webs.html
Access to this interactive links box is free online.

TIMELINE

Pharmacogenetics – five decades of therapeutic lessons from genetic diversity

Urs A. Meyer

Abstract | Physicians have long been aware of the subtle differences in the responses of patients to medication. The recognition that a part of this variation is inherited, and therefore predictable, created the field of pharmacogenetics fifty years ago. Knowing the gene variants that cause differences among patients has the potential to allow 'personalized' drug therapy and to avoid therapeutic failure and serious side effects.

Pharmacogenetics (PGx) deals with genetically determined variation in how individuals respond to drugs . Observations implying that genetic variation was responsible for the diversity in some drug responses were already being made five decades ago. We now know that the therapeutic failure of drugs as well as serious adverse side effects of drugs on individuals or subpopulations of patients can both have a genetic component. The toll that such variation takes in terms of individual suffering, high healthcare costs, and even lives, is increasingly being recognized. Recent developments in genomics, and associated technological innovations, have invigorated the study of such variation. Pharmacogenetic research has seen an explosion of interest by physicians, geneticists and the pharmaceutical industry — as reflected in the rapid increase in the number of publications that contain this term (FIG. 1). PGx has the potential to identify the particular drug and the dose of drug that is most likely to be effective and safe for each patient. This has become one of the main goals of modern drug therapy, and is frequently described as 'personalized medicine'. But in spite of its importance in explaining the diversity of responses to drugs, the integration of PGx into clinical practice has met considerable challenges.

The history of PGx reflects the evolution of human genetics and genomics, of molecular pharmacology and modern drug therapy. The field has had its visionaries and godfathers, who realized its importance early in its history. These early pioneers laid the foundations for the landmark discoveries that form the basis of present concepts and approaches (TIMELINE).

The gestation of a discipline

Sir Archibald Garrod, the perceptive physician-scientist. Around the year 1898 the British physician Archibald Garrod was interested in urinary pigments and studied patients at St. Bartholomew's Hospital in London that had ALCAPTONURIA (see Glossary) and patients that had PORPHYRIA that was caused by sulphonal (a hypnotic) [1,2]. Garrod was probably the first to realize the inherited predisposition of certain individuals to alcaptonuria[1] and other conditions. In particular,

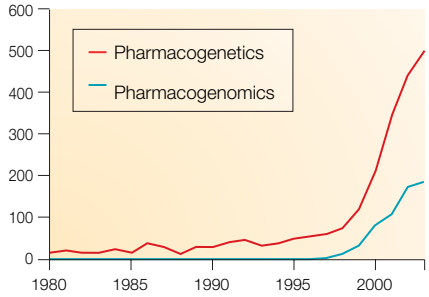


Figure 1 | **Appearance of the terms pharmacogenetics and pharmacogenomics in publications in PUBMED (National Library of Medicine).** Vogel first used the term pharmacogenetics (PGx) in 1959 (REF. 13). Publications on PGx have increased sharply in the last 5 years with the emergence of molecular genetics and genotyping technologies in clinical investigations. The term 'pharmacogenomics' first appeared in 1998.

With particular foresight Garrod went on to develop the concept of CHEMICAL INDIVIDUALITY in man, which was first presented in the Croonian Lectures around 1908 and then in *The Inborn Errors of Metabolism*[2] and in *The Inborn Factors of Disease*[4] (FIG. 2). His amazingly prescient vision of the basic tenets of PGx is summarized in the following passage: "Even against chemical poisons taken by mouth, or by other channels, there are some means of defence. Every active drug is a poison, when taken in large enough doses; and in some subjects a dose which is innocuous to the majority of people has toxic effects, whereas others show exceptional tolerance of the same drug. Some chemical poisons are destroyed in the tissues, provided that the dose given be not too large, and others are combined up with substances to hand, and so rendered innocuous and got rid of."[4].

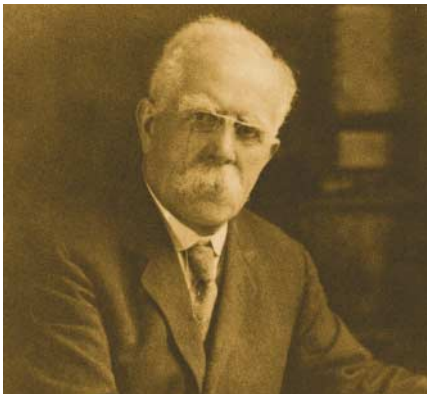
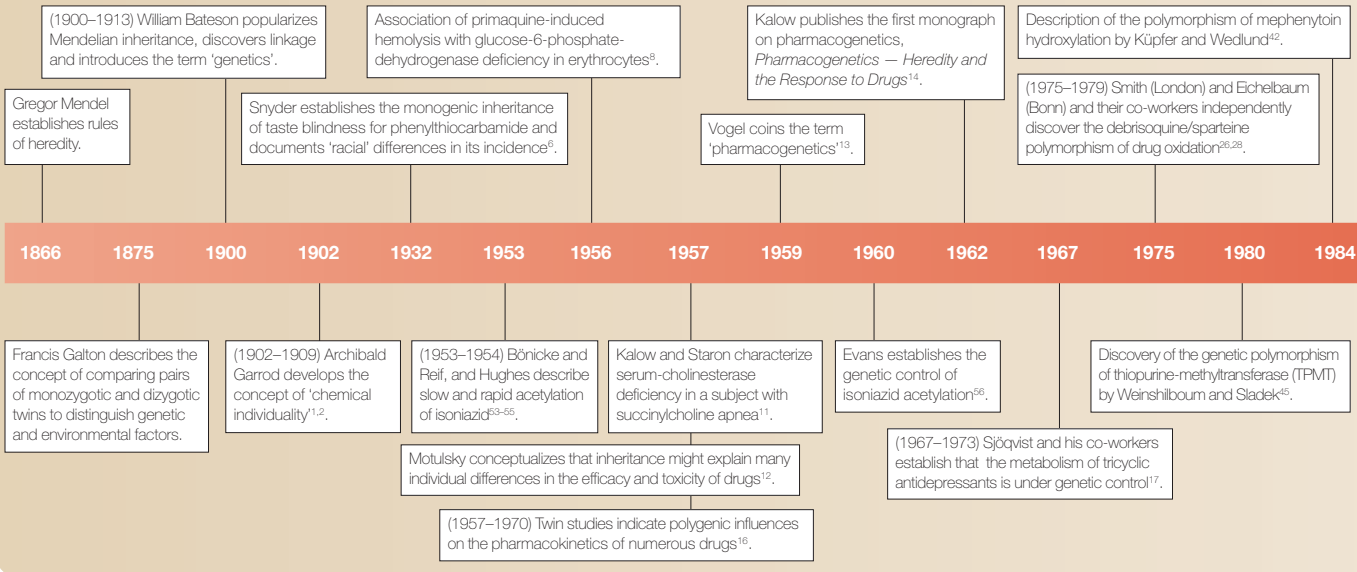


Figure 2 | **Sir Archibald E. Garrod (1958–1936).** Photograph taken by Simon Garrod in 1934. Modified from the cover of the monograph by Charles R. Scriver and Barton Childs on Garrod's book *The Inborn Factors Of Disease*[4]. Garrod coined the term 'chemical individuality'. Image reproduced with permission from REF. 63 © (1989) Oxford University Press.

Garrod observed that parental consanguinity was more common than usual among parents of children with alcaptonuria. Lore has it that Garrod recognized the Mendelian inheritance of alcaptonuria as a monogenic trait. This is unlikely, however, because Garrod was apparently unaware of the relationship between his observations and Mendel's work. It was probably William Bateson[3], another biologist who was ahead of his time, who interpreted Garrod's reports as recessive inheritance when he popularized Mendelian genetics in Britain. Bateson discovered genetic linkage and, in fact, introduced the term 'genetics' between 1902 and 1913.

Taste blindness: the first example of a pharmacogenetic study. Despite Garrod's insightful observation, the first experimental study that was of relevance to PGx was not of individual responses to a therapeutic drug: rather, it was of variation in the ability to taste a foreign chemical; specifically the inability to taste ('taste blindness' for) phenylthiocarbamide (PTC). While synthesizing chemicals in search for a sugar substitute, A. L. Fox[5] observed that some people detected the bitter taste of PTC when the crystals were placed on the tongue, whereas other people could detect only a very slight taste, or said it had the 'taste of sand'. L. H. Snyder[6], in an incredibly large study of 800 families, noted that this taste blindness was inherited in an autosomal-recessive fashion and that the frequency of non-tasters varied in populations of different ethnic origin or race. The molecular mechanism of 'taste blindness' for PTC and related substances — for example, propyl thiouracil — is unknown. Nonetheless, the study of 'taste blindness' was the prototype for future studies of pharmacogenetic variation. It was the first study of a common genetic polymorphism and it documented the association of race or ethnicity to a human response to chemicals.

Timeline | **A history of pharmacogenetics**



Landmark discoveries in the 1950s. The 1950s was the decade in which PGx emerged as a distinct discipline. New techniques allowed the more accurate measurement of enzyme activities, drug metabolites and drug responses. Although their significance was not recognised until late in the decade (see below), there were three clear examples of genetically determined variations in enzyme activity being shown to underlie adverse drug reactions, as Garrod predicted.

Alf Alving and co-workers observed that, in World War II, approximately 10% of African-American soldiers, but only a very small number of Caucasian soldiers, developed acute haemolytic crises when given an average dose of primaquine or other chemically related antimalarial drugs[7]. It was later shown that this sensitivity was caused by a deficiency of glucose 6-phosphate dehydrogenase (G6PD), which altered erythrocyte metabolism[8]. The same genetic defect was suspected to account for Favism — haemolysis after ingestion of Fava beans — which occurred in some individuals of Mediterranean descent. We now know that the *G6PD* locus on chromosome X is one of the most polymorphic genetic sites in humans. More than 400 million people carry one of 135 definitive *G6PD* variants and are at risk of haemolysis when exposed to drugs. The frequency of low-activity alleles of *G6PD* is highly correlated with the prevalence of malaria[9].

The drug succinylcholine (also known as suxamethonium), which is administered as an adjunct to anaesthesia, provided the second example of a genetic variant that causes an abnormal drug response — in this case prolonged APNEA[10]. Succinylcholine causes muscular paralysis, usually for a few minutes, but in exceptional cases for up to one hour. The prolonged effect is due to altered kinetics of a pseudocholinesterase (butyrylcholinesterase). Family studies showed that PSEUDOCHOLINESTERASE DEFICIENCY was inherited as an autosomal-recessive trait[11].

Perhaps the most well-known example of a genetic defect in drug biotransformation is the acetylation polymorphism. It was first observed with the advent of ISONIAZID therapy in tuberculosis in the 1950s and was shown 40 years later to be due to mutations in *N*-acetyltransferase-2 (*NAT2*) on chromosome 8 (BOX 1).

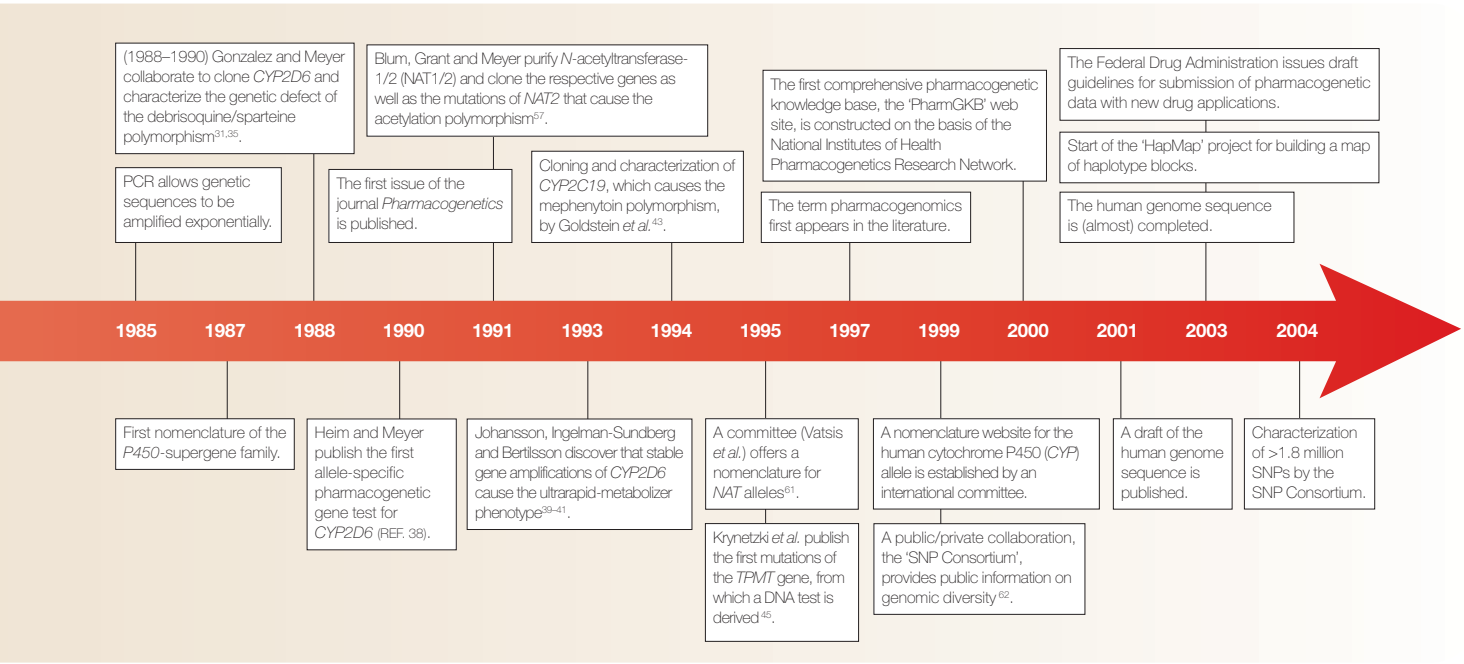
Box 1 | Acetylation polymorphism: prototype of variability in drug metabolism

Isoniazid, which was introduced in 1952, was the first drug that was effective in the treatment of tuberculosis. Bönike and Reif [53] in Germany, and Hughes in the United States[54] observed that, for any individual, urinary excretion of unchanged isoniazid was constant on repeated administration, but that there were marked differences in excretion among individuals. In later studies, Hughes determined that the differences were due to differences in the individual's ability to convert isoniazid to acetylisoniazid. 'Slow acetylators' were more prone to suffer from isoniazid toxicity, that is, PERIPHERAL NEUROPATHY[55]. Family studies showed this was an autosomal recessive trait. Subsequently, measurement of the plasma concentration of isoniazid 6 hours after an isoniazid dose allowed Evans[56] to identify two groups, rapid and slow acetylators.

These initial studies triggered many epidemiological, pharmacological and clinical studies in numerous countries, and provided a model of how pharmacogenetic traits could be analyzed. The acetylation polymorphism that was identified also affects the disposition of a variety of other drugs, including sulphonamides, dapsone (Avlosulfon; Wyeth Ayerst), phenelzine (Nardil; Pfizer Inc.), hydralazine, procainamide and numerous other foreign chemicals including chemical carcinogens. However it was not until 40 years later that the molecular causes of this polymorphism were elucidated[57,58]. Cloning of the cDNA that encodes the cytosolic enzyme *N*-acetyltransferase-2 in 1991 allowed identification of 2 common alleles[57]. These two alleles, were identified as restriction-fragment length polymorphisms and correspond to alleles now called *NAT2*5* and *NAT2*6*. These variants account for over 90% of slow-acetylator alleles[24]. As of June 2003, 14 mutations in the coding region of *NAT2* were described, which — alone or in various combinations — produce 36 different alleles (see Arylamine *N*-Acetyltransferase (NAT) Nomenclature in the online links box). Epidemiological studies have shown marked variability in the frequency of occurence of these alleles. The incidence of NAT2 slow acetylators might vary from 5 to 95%, depending on the population that is being studied[24]

Drug reactions, enzymes and genetics

In 1957 Arno Motulsky was the first to recognize the significance of the key discoveries of the 1950s. His seminal paper — *Drug reac-*



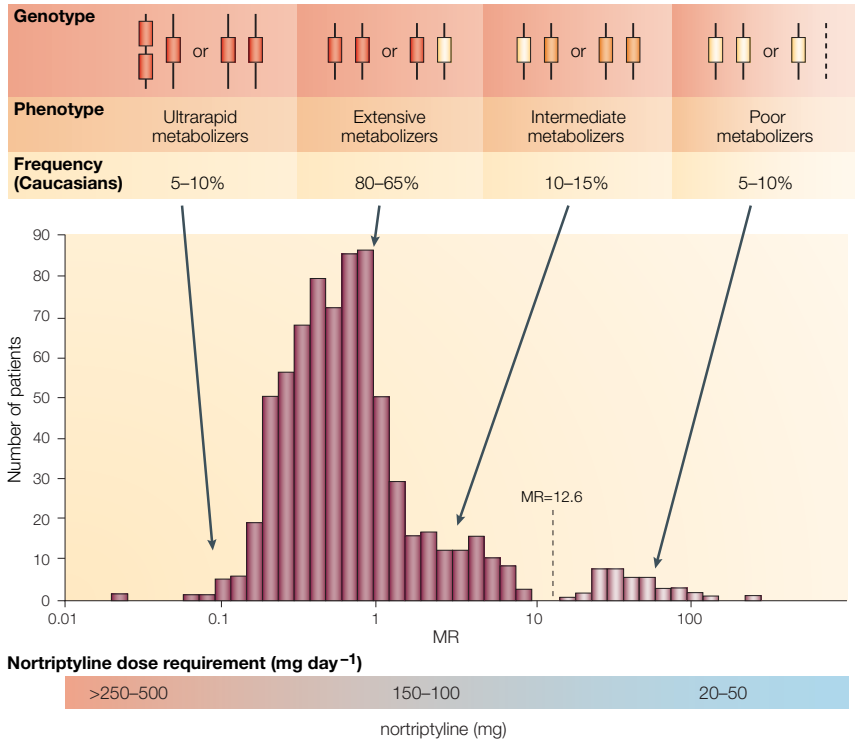


Figure 3 | **Genotype–phenotype relationships of the *CYP2D6*-polymorphism.** Null alleles of the *CYP2D6* gene on chromosome 22 are indicated by yellow boxes, fully functional alleles by red boxes, decreased function alleles by orange boxes, and deletion of the *CYP2D6* gene by a dashed line. The associated phenotypes and their approximate frequencies in Caucasian populations are assigned to the subpopulations that have been determined by the urinary metabolic ratio (MR) of debrisoquine to 4-hydroxy-debrisoquine. MR = 12.6 is the cutoff point between individuals with 'poor metabolism', as a result of decreased or absent CYP2D6 activity, and subjects with intermediate or extensive metabolism. To achieve the same plasma concentration of the antidepressant drug nortriptyline, poor metabolizers require only a fraction of the dose of extensive metabolizers, and ultrarapid metabolizers need a higher dose (modified from REFS 59,60).

tions, enzymes and biochemical genetics — was written on the invitation of a committee of the American Medical Association[12]. Motulsky highlighted the genetic basis of adverse reactions to both primaquine and succinylcholine (see above), but he also mentioned barbiturate-precipitated attacks of acute intermittent porphyria and hereditary HYPERBILIRUBINEMIA. He made the point that these reactions showed "how hereditary gene-controlled enzymatic factors determine why, with identical exposure, certain individuals become 'sick', whereas others are not affected." This paper marked the true beginnings of PGx as a distinct discipline. Recognition of the field spread rapidly. Friedrich Vogel in Heidelberg, Germany, coined the term 'pharmacogenetics' in 1959 (REF. 13). In 1962, Kalow published the first monograph on PGx[14], reviewing all the published examples of genetic factors that influence the response to drugs and chemicals. By 1956 a book with the title *'Biochemical Individuality'* already had a chapter on variability in the responses to drugs[15].

These publications triggered numerous observations over the following years on how genes affect drug responses, and a community of researchers that were interested in this topic started to develop. The first international conference on PGx, held at the New York Academy of Sciences, came in 1967. It brought together workers in many of the newly developing areas of pharmacogenetic research. In addition to G6PD deficiency these areas included MALIGNANT HYPERTHERMIA, FAMILIAL DYSAUTONOMIA, porphyria and red-blood-cell enzymatic defects that are associated with drug-induced haemolysis. Hereditary resistance to coumarin anticoagulants, reduced activity of alcohol dehydrogenase in the liver, adverse drug responses to acetophenetidin (METHEMOGLOBINEMIA and haemolysis) and genetic aspects of allergic reactions to drugs were other topics presented at that conference. They exemplify the wide spectrum and rising awareness of gene–drug interactions.

Regular symposia had a significant role in making PGx known to other disciplines, and many more pharmacogenetic conditions were observed in the following years. For example, starting in 1968, Vessell and co-workers used a series of identical and fraternal twins to assess the genetic contribution to the rate of disappearance of numerous drugs from plasma[16]. Alexanderson *et al.*[17] also used this approach to show the genetic control of steady-state plasma levels of NORTRIPTYLINE. These twin studies provided the most convincing evidence that, for many drugs, genetic factors underlie most of the variability in the rates of metabolism among different individuals. The modern statistical and genetic technologies to analyse such polygenic traits were not available at that time.

In parallel with the realization of the scope of pharmacological variation, more than 100 further examples of exaggerated responses to drugs, novel drug effects, or lack of effectiveness of drugs as a manifestation of inherited individual traits were documented in the 1980s (for reviews, see REFS 18–21). These examples also included a number of genetic disorders or enzymatic defects that predispose their otherwise healthy carriers to an abnormal, absent or adverse drug reaction, for example, WARFARIN resistance. Classic 'pharmacogenetic diseases' include inducible hepatic porphyrias and malignant hyperthermia. These disorders are uncovered or dramatically precipitated by the administration of drugs. Most of these inborn errors are rare, with the exception of G6PD deficiency.

Ecogenetics and toxicogenetics

Genetic variation also influences responses to any kind of environmental or xenobiotic impact (ecogenetics). Probably the first to point out the importance of ecogenetics was Brewer[22]. Ecogenetics is concerned with the dynamic interactions between an individual's genotype and environmental agents or toxicants such as industrial chemicals, pollutants, plant and food components, pesticides, and other chemicals. Examples of ecogenetic variation include differences between individuals in ethanol sensitivity, which is related to acetaldehyde-dehydrogenase deficiency; development of pulmonary emphysema in individuals with α_1-antitrypsin deficiency; and differences in nicotine metabolism that are associated with altered smoking behaviour[20,23]. The related field of toxicogenetics examines an individual's predisposition to carcinogenic, teratogenic, and other toxic effects of drugs and chemicals. Obviously, the principal concepts of PGx and ecogenetics are indistinguishable. The same applies to human variation in response to food components, for example, milk intolerance because of lactase deficiency.

Drug-metabolizing enzymes

Although the early landmarks of pharmacogenetic research concerned several relatively common deficiencies of drug-metabolizing enzymes such as *N*-acetyltransferase-2 (BOX 1) and pseudocholinesterase, the field was clearly invigorated by the discovery of the debrisoquine/sparteine polymorphism of drug oxidation in the 1970s. Two groups independently observed unexpected adverse reactions to these drugs in volunteers that were participating in PHARMACOKINETIC studies. Subsequent studies showed that both drugs are metabolized by the same enzyme, a cytochrome P450 monooxygenase that was later designated as CYP2D6. This enzyme affects the metabolism of numerous other drugs, including antidepressants, ANTI-ARRHYTHMICS and OPIOIDS (reviewed in REFS 24,25). The sometimes clinically dramatic manifestations and the unusual molecular genetics have made the debrisoquine/sparteine polymorphism one of the most well-studied pharmacogenetic traits, as reflected in over 2,500 publications since its discovery.

The CYP2D6 paradigm. In 1975, at St. Mary's Hospital Medical School in London, Robert L. Smith, the laboratory director, ingested 32 mg of debrisoquine, a SYMPATHICOLYTIC antihypertensive drug, as did some of his co-workers. His later account of his adverse response to the drug states: "Within two hours severe orthostatic hypotension set in with blood pressure dropping to 70/50 mm Hg, hypotensive symptoms persisted for up to two days after the dose…"[26]. His colleagues who had ingested a similar dose had no significant cardiovascular effects. Analysis of 4-hydroxydebrisoquine in the urine of the volunteers revealed that the extreme sensitivity was associated with the inability to form this metabolite. A later study of 94 medical students and 3 families who were given a dose of 10 mg of debrisoquine led to the description of this genetic polymorphism of drug oxidation with two phenotypes, the 'poor' and the 'extensive' metabolizers[27].

At the same time, in Bonn, Michel Eichelbaum and Hans Dengler were carrying out a routine pharmacokinetic study to characterize the kinetics of sparteine, an anti-arrhythmic and OXYTOXIC drug. Two individuals in the study had unpleasant side effects such as nausea, DIPLOPIA, blurred vision and headaches — symptoms that are typical of intoxication with this alkaloid. These adverse effects were associated with high plasma levels of sparteine. Subsequent population and family studies showed that sparteine metabolism was subject to a genetic polymorphism that results in two different phenotypes[28].

Both for debrisoquine and for sparteine, the metabolic defect was inherited in a Mendelian (monogenic) fashion as an autosomal-recessive trait. A few years later, the two independent observations converged when it became clear that they were the consequence of the same genetic metabolic deficiency.

The molecular mechanism of the debrisoquine/sparteine polymorphism was discovered a few years later. Biochemical studies in human liver microsomes first indicated that a deficiency of a specific cytochrome-P450 enzyme was responsible[29,30]. This enzyme was purified from human liver in the laboratory of F. P. Guengerich[31] and my own laboratory[32]. Uli Zanger in my laboratory next showed the absence of this protein in the livers of poor metabolizers of debrisoquine (or bufuralol)[33]. In the same year, in a collaboration with the laboratory of Frank Gonzalez at the National Cancer Institute/National Institutes of Health, the cDNA of this cytochrome-P450 enzyme, which was now called CYP2D6, was cloned[34]. This cDNA was used to show the inheritance of several defective alleles of *CYP2D6* by restriction-fragment length polymorphism (RFLP) analysis in several families of poor debrisoquine metabolizers[35]. A detailed sequence analysis of the two most frequent alleles (*CYP2D6*4* and *CYP2D6*3*) and the functional importance of each mutation was analyzed in heterologous expression experiments[36,37]. The timely emergence of PCR technology also allowed us to develop the first allele-specific PCR-test to identify the most common genotypes of poor metabolizers of debrisoquine[38].

Clinical observations and phenotyping of patients with debrisoquine 'urinary metabolic ratios' (FIG 3) in Sweden led to another interesting observations in 1993. Previously, Bertilsson *et al.*[39] had described an extremely high oxidation capacity for nortriptyline in a woman who was resistant to the normal doses of this antidepressant. Inger Johansson in Magnus Ingelman-Sundberg's laboratory detected unusual RFLP patterns in the DNA of the 'ultrarapid' metabolizers and found up to 12 extra copies of the *CYP2D6* gene fused in a head-to-tail orientation on chromosome 22 in these subjects[40]. Retrospective analysis of the DNA from the non-responder to antidepressant therapy also revealed that this patient was the carrier of three copies of *CYP2D6*[41]. This represents the first description of a stably amplified, functionally active, human gene, in which the amplification is inherited as dominant trait. However, not all of the ultrarapid metabolizers can be explained by gene duplication/amplification.

Since these discoveries, numerous additional *CYP2D6* alleles were discovered and their frequencies and functional significance were studied worldwide. The Home Page of the *CYP* allele nomenclature committee (see further information in the online links box) currently lists 44 alleles, including gene deletions and duplications, with a total number of 78 distinct variants. A number of these variants can be associated with four metabolism phenotypes: poor, intermediate, extensive and ultrarapid (FIG. 3).

The large number of important drug substrates for CYP2D6 has stimulated numerous studies of the genotype–phenotype rela-

Box 2 | Therapeutic lessons from pharmacogenetics

- All drug effects vary from person to person and all drug effects are influenced by genes.
- Most drug responses are multifactorial (that is, many genes and many environmental factors contribute to them).
- Genetic polymorphisms of single genes, including mutations in coding sequences, gene duplications, gene deletions and regulatory mutations affect numerous drug-metabolizing enzymes. Several cytochrome-P450 enzymes (for example, CYP2D6 and CYP2C9), *N*-acetyltransferases (NAT2), thiopurine methyltransferase (TPMT) and UDP-glucuronosyltransferases (UDP-GT) are examples. Individuals that possess these polymorphisms are at risk of experiencing documented adverse reactions or inefficacy of drugs at usual doses.
- Genetic polymorphisms of drug targets and drug transporters are increasingly recognized (receptors, ion channels, growth factors) as causing variation in drug responses.
- Several targets of cancer therapy, for example, the epidermal-growth-factor receptor, respond to treatment only in subgroups of patients who carry sensitizing mutations of these targets[48,49].
- The frequency of variation of drug effects, whether multifactorial or genetic, varies considerably in ethnically defined populations (for example, alleles of *N*-acetyltransferases)[24].
- Application of response-predictive genetic profiles (for example, genotyping for polymorphisms in antidepressant or cancer-drug therapy) on clinical outcomes has, so far, been done mostly in academic centers and has not yet reached clinical practice.

tionship of this polymorphism, as well as studies of disease associations and inter-ethnic variability. CYP2D6 seems to be the most variable and most well-investigated member of the cytochrome-P450 superfamily of genes.

Other drug-metabolizing enzymes. In the years after the discovery of the *CYP2D6* polymorphism, other polymorphisms of cytochrome-P450 genes were discovered, notably the MEPHENYTOIN polymorphism[42], which is due to a deficiency of CYP2C19 (REF. 43) and leads to an enhanced effect of the antiulcer drug omeprazole. The phenytoin/warfarin polymorphism, which is caused by mutations of *CYP2C9* (REF. 44), is another good example. This polymorphism affects the metabolism of the anticoagulant warfarin and the anticonvulsant phenytoin (Dilantin; Pfizer Inc.), as well as some other drugs.

In the decade that followed the elucidation of the mechanism of the *CYP2D6* polymorphism, many other genes that were responsible for such genetic polymorphisms were identified, functionally characterized, and linked to inherited differences in drug effects. One important example is the polymorphism of thiopurine *S*-methyltransferase (TPMT), with its clinically dramatic influence on the toxicity of the anticancer and immunosuppressive agents mercaptopurine and azathioprine (Imuran; GlaxoSmithKline). Other examples are the polymorphism of UDP-glucuronosyltransferase UGT1A1 and its effects on metabolism and toxicity of the anticancer drug irinotecan, and the deficiency of dihydropyrimidine dehydrogenase, which causes increased toxicity of the anticancer drug fluorouracil for a review of these topics, see REF. 45). Genotyping tests for *CYP2D6*, *TPMT*, *CYP2C9* and *UGT1A1* have been recommended to help make treatment decisions, but the routine use of genotyping is still in its infancy.

Transporters and drug targets. During the last 10 years, a number of polymorphisms of genes that encode drug transporters and drug targets have also been discovered and shown to alter drug responses (for review, see REFS 46,47). Of particular interest are the recent reports of the effectiveness of a generally ineffective drug, gefitinib (Iressa; AstraZeneca) in lung cancer patents that carry a sensitizing mutation of the epidermal growth factor receptor[48,49]. Such observations highlight the many sources of genetic variation that influence drug responses.

The challenge of multifactorial drug responses. At this time, the well-established examples of PGx with clinical relevance are pharmacogenetic diseases and genetic polymorphisms that alter the metabolism of drugs (BOX 2). All these are monogenic traits with Mendelian inheritance. However, most drug effects and treatment outcomes, or the individual risk for drug inefficacy or toxicity, are due to complex interactions between genes and the environment. Environmental variables include nutritional factors, concomitantly administered drugs, disease, and many other factors including lifestyle influences such as smoking and alcohol consumption. These factors work together with several individual genes that code for pharmacokinetic and PHARMACODYNAMIC determinants of drug effects such as receptors, ion channels, drug-metabolizing enzymes and drug-transporters. The challenge will be to define polygenic determinants of drug effects and to use a combination of genotyping and phenotyping tests to assess environmental influences[50]

Glossary

ALCAPTONURIA
A rare inherited disorder of metabolism that is characterized by urine which turns black when exposed to air.

ANTI-ARRHYTHMICS
Medicines that are used to treat patients who have irregular heart rhythms.

APNEA
The absence of breathing (respirations).

CHEMICAL INDIVIDUALITY
Garrod's influential idea that 'factors which confer upon us our predisposition and immunities from disease are inherent in our very chemical structure, and even in the molecular groupings which went to the making of the chromosomes from which we sprang.'

DIPLOPIA
Double vision. Usually due to misalignment of the eyes.

FAMILIAL DYSAUTONOMIA
A disorder of the autonomic nervous system that is inherited as an autosomal recessive trait and is characterized by several sensory deficits (as of taste and pain), excessive sweating and salivation, lack of tears, difficulty in swallowing and many other symptoms.

HYPERBILIRUBINEMIA
Abnormally high levels of bilirubin in the blood.

ISONIAZID
An anti-bacterial drug that has been used to prevent and to treat tuberculosis since 1952.

MALIGNANT HYPERTHERMIA
A group of inherited muscle problems characterized by muscle breakdown following certain stimuli — such as anesthesia, extremes of exercise (particularly in hot conditions), fever, or use of stimulant drugs. The problems associated with this condition result from over-excitable muscles that contract uncontrollably, severe fever, abnormal heart rhythms, and kidney failure.

MEPHENYTOIN
An anticonvulsant that is indicated for the treatment of tonic-clonic and partial seizures in patients who are not controlled with less-toxic medications.

METHEMOGLOBINEMIA
An inherited blood disorder that is characterized by increased levels of an abnormal form of haemoglobin that is unable to deliver oxygen effectively.

NORTRIPTYLINE
An antidepressant medication of the tricyclic class. Medications in this class are often referred to as tricyclic antidepressants, or TCAs.

OPIOIDS
Synthetic opium-like drugs that possess some affinity for any, or all, of the opioid-receptor subtypes. Common opioids are endorphin, fentanyl and methadone.

OXYTOXIC
A drug that is useful in starting or aiding in labour. Also used to stimulate uterine contractions.

PERIPHERAL NEUROPATHY
A problem in peripheral nerve function (any part of the nervous system except the brain and spinal cord) that causes pain, numbness, tingling, swelling, and muscle weakness in various parts of the body. Neuropathies might be caused by physical injury, infection, toxic substances, disease (for example, cancer, diabetes, kidney failure, or malnutrition), or drugs such as anticancer drugs.

PHARMACODYNAMICS
The process of interaction of pharmacologically active substances with target sites, and the biochemical and physiological consequences leading to therapeutic or adverse effects.

PHARMACOKINETICS
The rocess of the uptake of drugs by the body, the biotransformation they undergo, the distribution of the drugs and their metabolites in the tissues, and the elimination of the drugs and their metabolites from the body.

PORPHYRIA
A group of disorders that are characterized by the excessive production of porphyrins or their precursors, and which arise from abnormalities in the regulation of the porphyrin–heme pathway. Acquired pophyrias, which are due to inhibition of enzymes in the metabolic pathway by a drug, toxin or abnormal metabolite, are more common than those that are inherited.

PSEUDOCHOLINESTERASE DEFICIENCY
A rare genetic disorder that causes an absence of the plasma enzyme pseudocholinesterase, which can cause respiratory difficulty during surgery if the muscle-relaxing drug succinylcholine is used.

SYMPATHICOLYTIC
Interfering with, opposing, inhibiting, or destroying impulses from the sympathetic nervous system.

WARFARIN
An oral anticoagulant that inhibits the synthesis of clotting factors, thus preventing blood-clot formation.

Pharmacogenomics

The increasing use of the term pharmacogenomics (FIG. 1) reflects the evolution of PGx into the study of the entire spectrum of genes that determine drug responses, including the assessment of the diversity of the human genome sequence and its clinical consequences. There are three aspects of pharmacogenomics that make it different from classic PGx.

Genetic drug-response profiles. Rapid sequencing and genotyping of SNPs will have a significant role in associating sequence variations with heritable clinical phenotypes of drug or xenobiotic responses. SNPs occur approximately once every 300–3,000 bp if the genomes of 2 unrelated individuals are compared, and these represent 90–95% of all variant DNA sites. Any two individuals therefore differ at approximately 3–10 million bp, that is, <1% of the 3.2 billion bp of the haploid genome.

How can we use this information to predict drug responses? Pharmacogenomics focuses on SNPs for the simple and practical reason that they are both the most common and the most technically accessible class of genetic variations. For clinical-correlation studies in relatively small populations SNPs that occur at frequencies >10% are most likely to be useful, but rare SNPs with a strong selection component and a more marked effect on phenotype are equally important. Once a large number of these SNPs and their frequencies in different populations are known, they can be used to correlate an individual's genetic 'fingerprint' with their probable drug response. It has been proposed that high-density maps of SNPs or so-called haplotype blocks (sets of SNPs that are inherited together; see the International HapMap Project in the online links box) in the human genome might allow the use of these SNPs as markers of xenobiotic responses even if the target remains unknown, providing a 'drug-response profile' that is associated with contributions from many genes to a response phenotype. However, SNPs are not evenly distributed across the genome and differ between populations of different ethnic origin. In practice, therefore, and because of the complexities of defining disease phenotypes and clinical outcomes, the validity of this concept remains to be shown. Obviously, phenotyping methods will remain extremely important to assess the clinical relevance of genetic variations, as discussed below.

The effect of drugs on gene expression. Genomic technologies also include methods to study the expression of large groups of genes and indeed the entire complement of products (mRNAs) of a genome. Most drug actions produce changes in gene expression in individual cells or organs. This provides a new perspective for the way in which drugs interact with the organism and provides a measure of the biological effects of the drug. For instance, numerous drugs induce their own metabolism and the metabolism of other drugs by interacting with nuclear receptors such as AhR (arylhydrocarbon receptor), PPAR (peroxisome proliferator activated receptor), PXR (pregnane X receptor) and CAR (constitutive androstane receptor). These receptors function as 'xenosensors' and transcription factors that activate a response that includes increased biotransformation of drugs (reviewed in REF. 51). The phenomenon of induction has significant clinical consequences such as altered kinetics, drug–drug interactions or changes in hormone and carcinogen metabolism. Genomics is providing the technology to better analyze these complex multifactorial situations and to obtain individual genotypic and gene-expression information to assess the relative contributions of environmental and genetic factors to variations in drug responses.

Pharmacogenomics in drug discovery and drug development. The identification of all genes and, ultimately, the study of all protein variants that cause, contribute to, or modify a disease, will lead to new 'drugable' and 'nondrugable' targets, prognostic markers of disease states or severity-of-disease information. The pharmaceutical industry has realized this potential. It is obvious that the discovery of genes and proteins that are involved in the pathogenesis of disease allows the definition of new drug targets and promises to change profoundly the field of medicine in the future.

The promise of personalized medicine. Is the promise that pharmacogenomics will provide more 'personalized medicine' a reasonable expectation? And if so, why is PGx so rarely applied in clinical practice, in spite of well-established genetic polymorphisms and available genotyping methods? Numerous reasons for the slow acceptance of pharmacogenetic principles have been brought forward[46,50]. The lack of large prospective studies to evaluate the impact of genetic variation on drug therapy is one reason for the slow acceptance of these principles. On the other hand, pharmacogenetic information is increasingly included in product information or drug data sheets that alert the physician to dosing problems. Recent retrospective analysis of psychiatric patients that were treated with drugs that are substrates of CYP2D6 strongly indicates that genotyping can improve efficacy, prevent adverse drug reactions, and lower the costs of therapy with these agents[52]. The future impact of PGx and pharmacogenomics is likely to be considerable both in the selection of the right drug at the proper 'individual' dose and in the prevention of adverse effects (FIG. 3). By translating the increasing knowledge of human genetic diversity into better drug treatment, improved health through personalized therapy remains a realistic future scenario in many fields of medicine.

Urs A. Meyer is at the Biozentrum, University of Basel, CH-4056 Basel, Switzerland.
e-mail: Urs-A.Meyer@unibas.ch

doi:10.1038/nrg1428

1. Garrod, A. E. The incidence of alkaptonuria. A study in chemical individuality. *Lancet*, 1616–1620 (1902).
2. Garrod, A. E. *The inborn errors of metabolism*, (Oxford Univ. Press, London, UK, 1909).
3. Bateson, W. *Mendel's principles of heredity: A defence*, (Cambridge Univ. Press, Cambridge, UK, 1902).
4. Garrod, A. E. *The inborn factors of disease* (Oxford Univ. Press, London, UK, 1931).
5. Fox, A. L. The relationship between chemical constitution and taste. *Proc. Natl Acad. Sci. USA* **18**, 115–120 (1932).
6. Snyder, L. H. Studies in human inheritance IX. The inheritance of taste deficiency in man. *Ohio J. Sci.* **32**, 436–468 (1932).
7. Clayman, C. B. *et al.* Toxicity of primaquine in Caucasians. *J. Am. Med. Assoc.* **149**, 1563–1568 (1952).
8. Carson, P. E., Flanagan, C. L., Ickes, C. E. & Alving, A. S. Enzymatic deficiency in primaquine-sensitive erythrocytes. *Science* **124**, 484–485 (1956).
9. Luzatto, L., Mehta, A. & Vulliamy, M. Y. in *The Metabolic and Molecular Basis of Inherited Diseases* Vol. 3 (eds Scriver, C. R. *et al.*) 4517–4553 (McGraw–Hill Inc., New York, USA, 2001).
10. Lehmann, H. & Ryan, E. The familial incidence of low pseudocholinesterase level. *Lancet* **271**, 124 (1956).
11. Kalow, W. & Staron, N. On distribution and inheritance of atypical forms of human serum cholinesterase, as indicated by dibucaine numbers. *Can. J. Med. Sci.* **35**, 1305–1320 (1957).
12. Motulsky, A. Drug reactions, enzymes and biochemical genetics. *JAMA* **165**, 835–837 (1957).
13. Vogel, F. Moderne Probleme der Humangenetik. *Ergebn. Inn. Med. Kinderheilkd.* **12**, 52–125 (1959).
14. Kalow, W. *Pharmacogenetics: heredity and the response to drugs* (W. B. Saunders & Co., Philadelphia, USA, 1962).
15. Williams, R. J. *Biochemical Individuality*, (John Wiley & Sons, New York, USA, 1956).
16. Vesell, E. S. Twin studies in pharmacogenetics. *Hum. Genet.* **1**, (Suppl.) 19–30 (1978).
17. Alexanderson, B., Evans, D. A. & Sjoqvist, F. Steady-state plasma levels of nortriptyline in twins: influence of genetic factors and drug therapy. *Br. Med. J.* **4**, 764–768 (1969).
18. Price-Evans, D. A. in *Clinical and Molecular Pharmacogenetics* (Cambridge Univ. Press, Cambridge, UK, 1993).
19. Evans, W. E. & McLeod, H. L. Pharmacogenomics — drug disposition, drug targets, and side effects. *N. Engl. J. Med.* **348**, 538–549 (2003).
20. Weber, W. W. *Pharmacogenetics* 334 (Oxford Univ. Press, Oxford, UK, 1997).
21. Kalow, W., Meyer, U. A. & Tyndale, R. F. *Pharmacogenomics* (Marcel Dekker, New York and Basel, 2001).
22. Brewer, G. J. Annotation: human ecology, an expanding role for the human geneticist. *Am. J. Hum. Genet.* **23**, 92–94 (1971).
23. Sellers, E. M., Tyndale, R. F. & Fernandes, L. C. Decreasing smoking behaviour and risk through CYP2A6 inhibition. *Drug Discov. Today* **8**, 487–493 (2003).
24. Meyer, U. A. & Zanger, U. M. Molecular mechanisms of genetic polymorphisms of drug metabolism. *Annu. Rev. Pharmacol. Toxicol.* **37**, 269–296 (1997).
25. Zanger, U. M., Raimundo, S. & Eichelbaum, M. Cytochrome P450 2D6: overview and update on pharmacology, genetics, biochemistry. *Naunyn Schmiedebergs Arch. Pharmacol.* **369**, 23–37 (2004).

26. Smith, R. L. Introduction: human genetic variations in oxidative drug metabolism. *Xenobiotica* **16**, 361–365 (1986).
27. Mahgoub, A., Idle, J. R., Dring, L. G., Lancester, R. & Smith, R. L. Polymorphic hydroxylation of debrisoquine in man. *Lancet* **2**, 584–586 (1977).
28. Eichelbaum, M., Spannbrucker, N., Steincke, B. & Dengler, H. J. Defective *N*-oxidation of sparteine in man: a new pharmacogenetic defect. *Eur. J. Clin. Pharmacol.* **16**, 183–187 (1979).
29. Kahn, G. C., Boobis, A. R., Murray, S., Brodie, M. J. & Davies, D. S. Assay and characterisation of debrisoquine 4-hydroxylase activity of microsomal fractions of human liver. *Br. J. Clin. Pharmacol.* **13**, 637–645 (1982).
30. Meier, P. J., Mueller, H. K., Dick, B. & Meyer, U. A. Hepatic monooxygenase activities in subjects with a genetic defect in drug oxidation. *Gastroenterology* **85**, 682–692 (1983).
31. Distlerath, L. M. *et al*. Purification and characterization of the human liver cytochromes P-450 involved in debrisoquine 4-hydroxylation and phenacetin O-deethylation, two prototypes for genetic polymorphism in oxidative drug metabolism. *J. Biol. Chem.* **260**, 9057–9067 (1985).
32. Gut, J. *et al*. Debrisoquine-type polymorphism of drug oxidation: purification from human liver of a cytochrome P450 isozyme with high activity for bufuralol hydroxylation. *FEBS Lett.* **173**, 287–290 (1984).
33. Zanger, U. M., Hauri, H. P., Loeper, J., Homberg, J. C. & Meyer, U. A. Antibodies against human cytochrome P-450db1 in autoimmune hepatitis type II. *Proc. Natl Acad. Sci. USA* **85**, 8256–8260 (1988).
34. Gonzalez, F. J. *et al*. Characterization of the common genetic defect in humans deficient in debrisoquine metabolism. *Nature* **331**, 442–446 (1988).
35. Skoda, R. C., Gonzalez, F. J., Demierre, A. & Meyer, U. A. Two mutant alleles of the human cytochrome P-450db1 gene (*P450C2D1*) associated with genetically deficient metabolism of debrisoquine and other drugs. *Proc. Natl Acad. Sci. USA* **85**, 5240–5243 (1988).
36. Kagimoto, M., Heim, M., Kagimoto, K., Zeugin, T. & Meyer, U. A. Multiple mutations of the human cytochrome P450IID6 gene (*CYP2D6*) in poor metabolizers of debrisoquine. Study of the functional significance of individual mutations by expression of chimeric genes. *J. Biol. Chem.* **265**, 17209–17214 (1990).
37. Gough, A. C. *et al*. Identification of the primary gene defect at the cytochrome P450 *CYP2D* locus. *Nature* **347**, 773–776 (1990).
38. Heim, M. & Meyer, U. A. Genotyping of poor metabolisers of debrisoquine by allele-specific PCR amplification. *Lancet* **336**, 529–532 (1990).
39. Bertilsson, L., Aberg-Wistedt, A. & Gustaffson, L. L. Extremely rapid hydroxylation of debrisoquine; a case report with implication for treatment with nortriptyline and other tricyclic antidepressants. *Ther. Drug. Monit.* **7**, 478–480 (1985).
40. Johansson, I. *et al*. Inherited amplification of an active gene in the cytochrome P450 *CYP2D* locus as a cause of ultrarapid metabolism of debrisoquine. *Proc. Natl Acad. Sci. USA* **90**, 11825–11829 (1993).
41. Bertilsson, L. *et al*. Molecular basis for rational megaprescribing in ultrarapid hydroxylators of debrisoquine. *Lancet* **341**, 63 (1993).
42. Küpfer, A. & Preisig, R. Pharmacogenetics of mephenytoin: a new drug hydroxylation polymorphism in man. *Eur. J. Clin. Pharmacol.* **26**, 753–759 (1984).
43. de Morais, S. M. F. *et al*. Identification of a new genetic defect responsible for the polymorphism of *S*-mephenytoin metabolism in Japanese. *Mol. Pharmacol.* **46**, 594–598 (1994).
44. Sullivan-Klose, T. H. *et al*. The role of the CYP2C9-Leu359 allelic variant in the tolbutamide polymorphism. *Pharmacogenetics* **6**, 341–349 (1996).
45. Weinshilboum, R. Inheritance and drug response. *N. Engl. J. Med.* **348**, 529–537 (2003).
46. Goldstein, D. B., Tate, S. K. & Sisodiya, S. M. Pharmacogenetics goes genomic. *Nature Rev. Genet.* **4**, 937–947 (2003).
47. Roden, D. M. & George, A. L. Jr. The genetic basis of variability in drug responses. *Nature Rev. Drug Discov.* **1**, 37–44 (2002).
48. Lynch, T. J. *et al*. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. *N. Engl. J. Med.* **350**, 2129–2139 (2004).
49. Paez, J. G. *et al*. EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. *Science* **304**, 1497–1500 (2004).
50. Nebert, D. W., Jorge-Nebert, L. & Vesell, E. S. Pharmacogenomics and 'individualized drug therapy': high expectations and disappointing achievements. *Am. J. Pharmacogenomics* **3**, 361–370 (2003).
51. Handschin, C. & Meyer, U. A. Induction of drug metabolism: the role of nuclear receptors. *Pharmacol. Rev.* **55**, 649–673 (2003).
52. Chou, W. H. *et al*. Extension of a pilot study: impact from the cytochrome P450 2D6 polymorphism on outcome and costs associated with severe mental illness. *J. Clin. Psychopharmacol.* **20**, 246–251 (2000).
53. Bönicke, R. & Reif, W. Enzymatische Inaktivierung von Isonicotinsäure hydrazide im menschlichen und tierischen Organismus. *Arch. Exp. Pathol. Pharmakol.* **220**, 321–333 (1953).
54. Hughes, H. B., Biehl, J. P., Jones, A. P. & Schmidt, L. H. On the metabolic fate of isoniazid. *J. Pharmacol. Exp. Therap.* **109**, 444–452 (1953).
55. Hughes, H. B., Biehl, J. P., Jones, A. P. & Schmidt, L. H. Metabolism of isoniazid in man as related to the occurrence of peripheral neuritis. *Am. Rev. Tuberc.* **70**, 266–273 (1954).
56. Evans, D. A. P., Manley, F. A. & McKusick, V. A. Genetic control of isoniazid metabolism in man. *Br. Med. J.* **2**, 485–491 (1960).
57. Blum, M., Demierre, A., Grant, D. M., Heim, M. & Meyer, U. A. Molecular mechanism of slow acetylation in man. *Proc. Natl Acad. Sci. USA.* **88**, 5237–5241 (1991).
58. Vatsis, K. P., Martel, K. J. & Weber, W. W. Diverse point mutations in the human gene for polymorphic *N*-acetyltransferase. *Proc. Natl Acad. Sci. USA* **88**, 6333–6337 (1991).
59. Meyer, U. A. Pharmacogenetics and adverse drug reactions. *Lancet* **356**, 1667–1671 (2000).
60. Kirchheiner, J. *et al*. Individualized medicine — implementation of pharmacogenetic diagnostics in antidepressant drug treatment of major depressive disorders. *Pharmacopsychiatry* **36** (Suppl. 3), S235–S243 (2003).
61. Vatsis, K. P. *et al*. Nomenclature for *N*-acetyltransferases. *Pharmacogenetics* **5**, 1–17 (1995).
62. Masood, E. A. A consortium plans free SNP map of human genome. *Nature* **398**, 545–546 (1999).
63. Scriver, C. R. & Childs, B. (eds) *Garrod's Inborn Factors Of Disease* (Clarendon Press, Oxford, UK, 1989).

Acknowledgments

Research in the author's laboratory is supported by the Swiss National Science Foundation.

Competing interests statement

The author declares no competing financial interests.

Online links

DATABASES

The following terms in this article are linked online to:

Entez: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi
AhR | CAR | *CYP2C9* | CYP2C19 | CYP2D6 | G6PD | *NAT2* | TPMT | UGT1A1

Home Page of the *CYP* Allele Nomenclature Committee: http://www.imm.ki.se/CYPalleles/

International HapMap Project: http://www.hapmap.org

Arylamine *N*-Acetyltransferase (NAT) Nomenclature: www.louisville.edu/medschool/pharmacology/NAT.html

Access to this links box is available online.

VIEWPOINT

Pharmacogenetics: ethical problems and solutions

Alasdair Breckenridge, Klaus Lindpaintner, Peter Lipton, Howard McLeod, Mark Rothstein and Helen Wallace

Abstract | Regulators, drug companies, academic scientists, bioethicists, clinicians and, increasingly, the general public are starting to realize that pharmacogenetics (PGx) will probably have a huge impact on the way in which we treat both common and rare diseases. But how much thought has gone into the ethical issues that the incorportation of phamacogenetic testing into drug discovery, prescription and use will entail? It seems that "quite a bit" is the answer, as the diverse viewpoints of representatives of all of these groups presented here illustrate. However, these views also highlight that now is the time to start formulating and implementing solutions to these potential problems.

What do you see as the most important future benefits of PGx to society and, conversely, what are the main problems that it poses?

• Individuals differ in their response to medicines for many reasons, one of the most important being differences in their genetic make-up. PGx is the study of genetic variations that affect responses to medicines, both in terms of efficacy and safety. For certain medicines, appropriate genetic testing could, in theory, select those patients who are likely to derive more benefit from a medicine or, conversely, those who are more likely to suffer an adverse effect. This has implications not only for individual treatment, but also for the way in which medicines are developed. Clinical trials of new medicines conducted in cohorts of patients selected by PGx testing could be smaller and could be carried out more quickly, which would result in lower development costs. Evaluation of the safety profile of medicines that are already on the market is also an important area in which PGx profiling can be used.

Much is made of how this approach raises concerns about patient confidentiality and