

Pharmacogenomics Education: International Society of Pharmacogenomics Recommendations for Medical, Pharmaceutical, and Health Schools Deans of Education

D Gurwitz¹, JE Lunshof², G Dedoussis³, CS Flordellis⁴, U Fuhr⁵, J Kirchheiner⁵, J Licinio⁶, A Llerena⁷, VG Manolopoulos⁸, LJ Sheffield⁹, G Siest¹⁰, F Torricelli¹¹, V Vasiliou¹² and S Wong¹³

¹Department of Human Genetics & Molecular Medicine, Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel; ²Section Community Genetics, Department of Clinical Genetics & Human Genetics, VU University Medical Center, Amsterdam, The Netherlands; ³Harokopio University of Athens, Athens, Greece; ⁴Department of Pharmacology, University of Patras Medical School, Patras, Greece; ⁵Department of Pharmacology, Clinical Pharmacology Unit, University of Cologne, Germany; ⁶David Geffen School of Medicine, UCLA, Los Angeles, CA, USA; ⁷Department of Pharmacology and Psychiatry, University of Extremadura Medical School, Spain; ⁸Laboratory of Pharmacology, Medical School, Democritus University of Thrace, Alexandroupolis, Greece; ⁹Genetic Health Services Victoria, Murdoch Childrens Research Institute, University of Melbourne, Melbourne, Australia; ¹⁰Faculty of Pharmacy, INSERM U.525, University Henri Poincaré Nancy 1, Nancy, France; ¹¹Laboratory of Genetics, Hospital-University Careggi, Florence, Italy; ¹²University of Colorado Health Sciences, Denver, CO 80262, USA; ¹³Clinical Chemistry/Toxicology, TDM, Pharmacogenomics, and Proteomics, Medical College of Wisconsin, Milwaukee, WI, USA

Correspondence:

D Gurwitz, Department of Human Genetics & Molecular Medicine, Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel. E-mail: gurwitz@post.tau.ac.il and JE Lunshof, Section Community Genetics, Department of Clinical Genetics & Human Genetics, VU University Medical Center, Amsterdam, The Netherlands. E-mail: je.Lunshof@vumc.nl

Received: 2 February 2005
Accepted: 25 February 2005
Published online 26 April 2005

ABSTRACT

Pharmacogenomics would be instrumental for the realization of personalized medicine in coming decades. Efforts are evident to clarify the potential bioethical, societal, and legal implications of key pharmacogenomics-based technologies projected to be soon introduced into the core practice of medicine. In sharp contrast, a lack of sufficient attention to educational aspects of pharmacogenomics, both for professionals and for society at large, is evident. In order to contribute to this discussion, a 'Pharmacogenomics Education Forum' was held on October 2, 2004 during the 3rd Annual Meeting of the International Society of Pharmacogenomics (ISP) at Santorini, Greece. The participants, members of the ISP Pharmacogenomics Education Forum, after deliberate discussions, proposed a document of 'Background Statement' and 'Recommendations and Call for Action' addressed to Deans of Education at Medical, Pharmaceutical, and Health Schools globally. This document has been considered by the education committee of the International Society of Pharmacogenomics and the result is presented here. We hope that this call would be listened to, and soon followed by beneficial action, ultimately leading to enhanced implementation of personalized medicine into core medical education and practice.

The Pharmacogenomics Journal (2005) 5, 221–225. doi:10.1038/sj.tpj.6500312; published online 26 April 2005

Keywords: pharmacogenetics; education; continuing medical education; personalized medicine; adverse drug reactions (ADRs); cytochrome P450 enzymes; thiopurine methyltransferase (TPMT); International Society of Pharmacogenomics (ISP)

INTRODUCTION

Pharmacogenetics, the union of classical pharmacology with human genetics, together with the more wide-ranging discipline of pharmacogenomics, which encompasses novel gene expression profiling, proteomics, and bioinformatics tools, present a valuable potential for implementation into the practice of medicine.^{1–6} New pharmacogenomics knowledge would allow the incorporation of individualized or personalized medicine to the clinic, most likely starting with comprehensive reductions in the alarmingly high rates of adverse drug reactions (ADRs), currently estimated to account for about 6% of new hospital admissions to internal medicine wards.^{7–9} Meanwhile, tools for rapid genotype-based

identification of individuals likely to be 'poor or ultra-rapid metabolizers' for certain cytochrome P450 enzymes are already entering the diagnostics market.¹⁰ Such individuals metabolize certain drugs much slower or much faster than normally due to genetic fault or presence of extra copies of the relevant cytochrome P450 gene. For example, individuals who are 'CYP2D6 poor or ultra-rapid metabolizers' metabolize many antipsychotic and antidepressant drugs at very slow or too rapid rates, respectively. For 'CYP2D6 poor metabolizers' this puts them at elevated risk for ADR,¹¹⁻¹³ while for the 'CYP2D6 ultra-rapid metabolizers' this often leads to lack of drug efficacy.^{13,14} The antipsychotic and antidepressant drugs are among the most frequently prescribed worldwide. Consequently, harmful blood concentrations of such drugs might occur even when taken at recommended dosage, and ADRs are therefore likely to take place.⁴⁻⁶ Thus, it is of utmost importance to identify such at-risk individuals in advance as a vital part of the quest to reduce the incredibly high current ADR rates, which have become a major cause of morbidity and mortality in developed nations.⁷⁻⁹

In coming decades, personalized medicine is expected to methodically revolutionize the practice of most medical disciplines, offering more efficacious pharmacotherapy possible for the individual patient based primarily on genetic profiling.^{15,16} The key questions now seem to be not if true personalized medicine would arrive at the clinic, but rather, when it would arrive, and how it would affect the well being both of individuals and of society.^{5,6} Obviously, the move towards pharmacotherapy decisions, based to a great deal on the patient's individual genome, expression profiling, or proteome data, would dramatically affect the way that medicine is practiced, posing substantial moral concerns.¹⁷⁻²⁵ Discussions are well under way regarding medical, ethical, societal, and regulatory aspects of pharmacogenomics and its expected implementation into the clinic.¹⁷⁻²⁵ Entire public conferences have been devoted to bioethics and societal aspects of pharmacogenomics, including special working parties such as those set by the Nuffield Council on Bioethics²⁶ and the European Commission.²⁷

In contrast to the extensive on-going interest of leaders of the medical community in bioethics and societal aspects of pharmacogenomics, expressed in debates and publications,¹⁷⁻²⁵ there appears to be a relative lack of initiatives concerning the educational aspects of pharmacogenomics, both for professionals and for the community.⁶ Clearly, we are facing an urgent need to better educate our future physicians, so that they would be able to fully utilize the potential of the new diagnostics tools that are already arriving at the clinic for improving drug safely.¹⁰ Although several calls advocating for its incorporation into the pharmacy schools²⁸⁻³¹ and medical schools curricula^{16,32} have been made, a recent provisional survey prepared by one of us (DG) during the summer of 2004 and presented at the 3rd Annual ISP Meeting found that only a minority of medical schools in Europe and North America already include pharmacogenomics as part of their core

pharmacology curricula. This situation might reflect insufficient alertness of those in charge of updating the medical education curricula, possibly combined with the tendency of medical faculty to be conservative,³³ and a lack of appropriate pharmacology textbook chapters.

In order to move forward with the incorporation of pharmacogenomics into the medical schools core curricula, a 'Pharmacogenomics Education Forum' was held during the October 2004 3rd Annual Meeting of the International Society of Pharmacogenomics (ISP) at Santorini Island, Greece.⁶ The participants, members of the ISP Pharmacogenomics Education Forum, after focused discussions during the conference and followed by correspondence, agreed upon the following 'Background Statement' and 'Recommendations and Call for Action' to Deans of Education at Medical, Pharmaceutical, and Health Schools globally.

ISP PHARMACOGENOMICS EDUCATION FORUM BACKGROUND STATEMENT

1. We perceive pharmacogenomics to be one of the key platforms for personalized medicine, which will ultimately allow safer and more effective pharmacotherapy for many chronic ailments in particular. Personalized medicine will be based in large part on each patient's unique genome, and/or unique gene expression profiling or proteomics data of blood samples or biopsy specimens of the diseased tissues. Such information would include variations in alleles and expression levels of drug-metabolizing enzymes, drug transporters, drug target genes, disease risk genes, and protective (disease-modifying) genes.
2. We are aware that pharmacogenomics is a rapidly evolving research field, where many observations need further substantiation in larger study cohorts, and in additional ethnic and other subgroups. Yet, it already embraces several established observations and technologies ready for immediate clinical implementation. One notable example is genotyping for CYP2D6 and CYP2C19 alleles associated with 'poor drug metabolizer' phenotypes, for which clinical guidelines with adjusted dose recommendations for several antidepressants have been published,³⁴ and in September 2004 the EU has approved the first commercial DNA chip for clinical diagnosis.¹⁰
3. We view with concern the fact that the implementation of personalized medicine is much slower than anticipated. Six years ago, a report by the Institute of Medicine stated that up to 100 000 people in the US alone died each year of medical errors, a large part of which reflecting toxic drug reactions.³⁵ Thousands of human lives can potentially be saved each year if certain aspects of pharmacogenomics, such as cytochrome P450 enzymes genotyping, are adopted by treating physicians, get widely implemented into the clinic, and become a common ingredient of medical practice worldwide. Indeed, in a recent poll conducted by the American Association for Clinical Chemistry, five cytochrome P450

genes (CYP2D6, CYP2C9, CYP2C19, CYP2B6, and CYP3A5) were identified among the 'top 10 pharmacogenetic tests'.³⁶ Of note, thiopurine methyltransferase (TPMT) was identified as the second most important pharmacogenetic test following CYP2D6 on this list. Safe and effective pharmacotherapy, prescribed following genotyping for these enzymes, would contribute significantly to the improvement of quality of life and reduction of ADRs associated with drugs metabolized by these enzymes.

4. We are aware that a true and all-binding personalized medicine might be decades away, and harbors some controversial ethical and legal questions that will need to be continuously discussed and solved through public debate and legislation. Many open questions on pharmacoconomics remain without clear answers. For example, who will pay the high projected costs for revised drug labeling information, needed for many current drugs, scores of which are generics and of little interest for the pharmaceutical industry?
5. We are also aware that initial unrestricted optimism on the potential of pharmacogenomics has been recently sobered by more skeptical views.^{37,38} However, the above examples of the ability to predict poor metabolizers for a substantial number of drugs should not be ignored. We therefore expect that pharmacogenomics will soon find an increasing place in medical practice and therefore current skepticism should not hamper efforts for teaching the basics of pharmacogenomics to current students of healthcare professions, using the up-to-date corroborated scientific knowledge. Our medical, nursing, pharmacy, pharmacology, medical biology, and health administration students should be able to comprehend pharmacogenomics foundations and principles by the time they finish their internships or graduate studies. This would be essential for enabling them to manage the new genomics-based diagnostic tools and techniques, and related decision-taking paradigms governing state-of-the-art patient care. Certain aspects of personalized medicine, most likely beginning with genomic tools for improved drug safety, will definitely arrive at the clinic by the time that they conclude their specialization in various medical disciplines, or as they begin their independent careers as healthcare professionals. Moreover, diagnostics companies are actively developing rapid pharmacogenomics 'point of care' tests. It is predicted that several such '1 h tests' would appear on the diagnostics market by 2007 (Janet Warrington, Affymetrix, personal communication). This will allow a major move forward with the realization of personalized medicine, including at the emergency room setting. It is essential for good medical practice to have physicians and health professionals who would know how to make the best use of such diagnostics once they are in the market. Unless health educators start teaching pharmacogenomics soon, the expected benefit to society from such novel tools will be slower to implement, at the cost of unnecessary human morbidity and mortality.

ISP RECOMMENDATIONS AND CALL FOR ACTION

The following recommendations were arrived at during discussions at the 'Pharmacogenomics Education Forum' held at the October 2004 3rd Annual ISP Meeting, and in subsequent correspondence between the forum participants.

1. We call upon Deans of Education at Medical, Pharmaceutical, and Health Schools worldwide to incorporate the teaching of pharmacogenomics as an integral part of their core pharmacology curricula, as soon as possible.
2. We call upon policymakers and government agencies involved with medical education, and education sections of National Pharmacology Societies, and the European and International Pharmacology Organizations to recommend the incorporation of the teaching of pharmacogenomics globally in the basic education of physicians, pharmacists, and nurses.
3. Basic MD pharmacogenomics education should ideally encompass at least 4 h, and ideally about 8 h of teaching, as part of the basic pharmacology curricula for MD students. It should include background information on the large scope of human genome variation and on the scientific methods employed to utilize this variation for the benefit of medical practice. It should emphasize the potential of pharmacogenomics applications for improving the quality and safety of pharmacotherapy for chronic diseases in several organ systems. Finally, it should present in detail common genetic polymorphisms in drug-metabolizing enzymes affecting drug pharmacokinetics and hence drug safety, such as the CYP450 enzyme family and the TPMT. Examples of polymorphisms that seem to affect drug pharmacodynamics, such as the beta-2 adrenergic receptor and apolipoprotein E, should also be taught. This might be incorporated as a case-based learning module in pharmacology/toxicology or pathology courses.
4. More extensive teaching in pharmacogenomics should be offered to graduate students in Pharmaceutical, Life Sciences, and Health Schools.³²
5. Pharmacogenomics is a rather new field that has not been part of the curricula of practicing clinicians today. Efforts for continuing medical education (CME) on pharmacogenomics should be initiated in major academic hospitals worldwide.
6. Oncology teaching and CME programs, in particular, must include a focused emphasis on pharmacogenomics, since personalized, genotype-based treatments have effectively entered the clinic for several types of malignancies.
7. The content of pharmacogenomics educational material should be updated regularly, keeping up-to-date with the latest developments and technical innovations.
8. We call upon publishers of basic and clinical pharmacology textbooks to dedicate a separate chapter to pharmacogenomics in their upcoming editions. Meanwhile, review articles, web resources, and case studies should be employed as teaching materials.

9. We call upon individuals in charge of agencies controlling national healthcare systems, as well as leaders of the pharmaceutical industry, to assist in the creation of pharmacogenomics education tools for healthcare professionals, by allocating funds towards the design and distribution of adequate teaching materials. Ideally, this should include the creation of open-access comprehensive web-based tutorials, including frequently updated online lectures, presentations, and manuscripts. This will, in the long run, benefit not only the population and especially those in need of adequate individualized pharmacotherapy but also governments, by substantially reducing health care costs and hospitalizations due to adverse drug reactions.⁷⁻⁹
10. Better pharmacogenomics education for healthcare professionals, combined with better patient education by treating physicians, is ultimately required for the coming genomic transformation in the practice of most medical disciplines. Eventually, such didactic efforts will amount to better public awareness, and to the advancement of both individual and community health.

CONCLUSIONS

The participants of the 'Pharmacogenomics Education Forum' held on October 2, 2004 during the 3rd Annual Meeting of the International Society of Pharmacogenomics (ISP) and the Education Sub committee of the ISP issue the above 'Background Statement' and 'Recommendations and Call for Action' addressed to Medical, Pharmaceutical, and Health Schools Deans of Education. We call upon Deans of Education to incorporate pharmacogenomics in the core teaching curricula of pharmacology without further delay. Taking this step now is vital for ensuring successful implementation of personalized medicine into medical practice later, in pace with the emergence of the latest genomic diagnostics tools, for the benefit of the individual patient and society at large. Unless this step is soon taken, medical education might later become a bottleneck in the road to implement personalized medicine. Education for the next generation is a prime community task concerning all disciplines of knowledge. Wherever medicine is concerned, this task is also an asset for the present generation, as our current health professions students will take care of our generation when it ages.

DUALITY OF INTEREST

None declared.

REFERENCES

- 1 Evans WE, Relling MV. Moving towards individualized medicine with pharmacogenomics. *Nature* 2004; **429**: 464-468.
- 2 Meyer UA. Pharmacogenetics—five decades of therapeutic lessons from genetic diversity. *Nat Rev Genet* 2004; **5**: 669-676.
- 3 Siest G, Jeannesson E, Berrahmoune H, Maumus S, Marteau JB, Mohr S et al. Pharmacogenomics and drug response in cardiovascular disorders. *Pharmacogenomics* 2004; **5**: 779-802.
- 4 Weinsilboum R, Wang L. Pharmacogenomics: bench to bedside. *Nat Rev Drug Discov* 2004; **3**: 739-748.
- 5 Gurwitz D, Weizman A. Personalized psychiatry: a realistic goal. *Pharmacogenomics* 2004; **5**: 213-217.
- 6 Frueh FW, Gurwitz D. From pharmacogenetics to personalized medicine: a vital need for educating health professionals and the community. *Pharmacogenomics* 2004; **5**: 571-579.
- 7 Pirmohamed M, James S, Meakin S, Green C, Scott AK, Walley TJ et al. Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients. *BMJ* 2004; **329**: 15-19.
- 8 Dormann H, Criegee-Rieck M, Neubert A, Egger T, Geise A, Krebs S et al. Lack of awareness of community-acquired adverse drug reactions upon hospital admission: dimensions and consequences of a dilemma. *Drug Saf* 2003; **26**: 353-362.
- 9 Dormann H, Neubert A, Criegee-Rieck M, Egger T, Radespiel-Troger M, Azaz-Livshits T et al. Readmissions and adverse drug reactions in internal medicine: the economic impact. *J Intern Med* 2004; **255**: 653-663.
- 10 Roche Press Release. First chip-based test for broad diagnostic use in European Union has CE mark. September 1, 2004. <http://www.roche.com/med-cor-2004-09-01>.
- 11 Brockmoller J, Kirchheiner J, Schmider J, Walter S, Sachse C, Muller-Oerlinghausen B et al. The impact of the CYP2D6 polymorphism on haloperidol pharmacokinetics and on the outcome of haloperidol treatment. *Clin Pharmacol Ther* 2002; **72**: 438-452.
- 12 Wuttke H, Rau T, Heide R, Bergmann K, Bohm M, Weil J et al. Increased frequency of cytochrome P450 2D6 poor metabolizers among patients with metoprolol-associated adverse effects. *Clin Pharmacol Ther* 2002; **72**: 429-437.
- 13 Kirchheiner J, Sasse J, Meineke I, Roots I, Brockmoller J. Trimipramine pharmacokinetics after intravenous and oral administration in carriers of CYP2D6 genotypes predicting poor, extensive and ultrahigh activity. *Pharmacogenetics* 2003; **13**: 721-728.
- 14 Kaiser R, Sezer O, Papies A, Bauer S, Schelenz C, Tremblay PB et al. Patient-tailored antiemetic treatment with 5-hydroxytryptamine type 3 receptor antagonists according to cytochrome P-450 2D6 genotypes. *J Clin Oncol* 2002; **20**: 2805-2811.
- 15 Langreth R, Waldholz M. New era of personalized medicine: targeting drugs for each unique genetic profile. *Oncologist* 1999; **4**: 426-427.
- 16 Ginsburg GS, McCarthy JJ. Personalized medicine: revolutionizing drug discovery and patient care. *Trends Biotechnol* 2001; **19**: 491-496.
- 17 Rothstein MA, Epps PG. Ethical and legal implications of pharmacogenomics. *Nat Rev Genet* 2001; **2**: 228-231.
- 18 Moldrup C. Ethical, social and legal implications of pharmacogenomics: a critical review. *Community Genet* 2001; **4**: 204-214.
- 19 Lipton P. Pharmacogenetics: the ethical issues. *Pharmacogenomics J* 2003; **3**: 14-16.
- 20 Wertz DC. Ethical, social and legal issues in pharmacogenomics. *Pharmacogenomics J* 2003; **3**: 194-196.
- 21 Winkelmann BR. Pharmacogenomics, genetic testing and ethnic variability: tackling the ethical questions. *Pharmacogenomics* 2003; **4**: 531-535.
- 22 Weijer C, Miller PB. Protecting communities in pharmacogenetic and pharmacogenomic research. *Pharmacogenomics J* 2004; **4**: 9-16.
- 23 van Delden J, Bolt I, Kalis A, Derijks J, Leufkens H. Tailor-made pharmacotherapy: future developments and ethical challenges in the field of pharmacogenomics. *Bioethics* 2004; **18**: 303-321.
- 24 Webster A, Martin P, Lewis G, Smart A. Integrating pharmacogenetics into society: in search of a model. *Nat Rev Genet* 2004; **5**: 663-669.
- 25 Breckenridge A, Lindpaintner K, Lipton P, McLeod H, Rothstein M, Wallace H. Pharmacogenetics: ethical problems and solutions. *Nat Rev Genet* 2004; **5**: 676-680.
- 26 Nuffield Council on Bioethics. Pharmacogenetics: ethical issues. 2003. http://www.nuffieldbioethics.org/fileLibrary/pdf/pharmacog_consultation.pdf.
- 27 European Commission 2004. Ethical, legal and social aspects of genetic testing: research, development and clinical applications. European Commission Expert Group. http://europa.eu.int/comm/research-conferences/2004/genetic/pdf/report_en.pdf.

- 28 Vizirianakis IS. Pharmaceutical education in the wake of genomic technologies for drug development and personalized medicine. *Eur J Pharm Sci* 2002; **15**: 243–250.
- 29 Brock TP, Faulkner CM, Williams DM, Smith SR. Continuing-education programs in pharmacogenomics for pharmacists. *Am J Health Syst Pharm* 2002; **59**: 722–725.
- 30 McCurdy CR. Pharmacy education: from Prescott to pharmacogenomics. *J Am Pharm Assoc (Wash)* 2002; **42**: 688–691.
- 31 Sansgiry SS. The future of pharmacy education: back to which basics? *Pharmacotherapy* 2004; **24**: 688–989.
- 32 Gurwitz D, Weizman A, Rehavi M. Education: teaching pharmacogenomics to prepare future physicians and researchers for personalized medicine. *Trends Pharmacol Sci* 2003; **24**: 122–125.
- 33 Watson RT, Suter E, Romrell LJ, Harman EM, Rooks LG, Neims AH. Moving a graveyard: how one school prepared the way for continuous curriculum renewal. *Acad Med* 1998; **73**: 948–955.
- 34 Kirchheiner J, Brosen K, Dahl ML, Gram LF, Kasper S, Roots I *et al*. CYP2D6 and CYP2C19 genotype-based dose recommendations for antidepressants: a first step towards subpopulation-specific dosages. *Acta Psychiatr Scand* 2001; **104**: 173–192.
- 35 Kohn L, Corrigan J, Donaldson M (eds). *To Err is Human. Building a Safer Health System*. Committee on Quality of Health Care in America. Institute of Medicine. National Academy Press: Washington, DC, 1999. http://books.nap.edu/html/to_err_is_human/.
- 36 Auxter-Parham S. Bringing pharmacogenomic assays to market. *Clin Lab News* 2004; **30**: 1–7.
- 37 Nebert DW, Jorge-Nebert L, Vesell ES. Pharmacogenomics and ‘individualized drug therapy’: high expectations and disappointing achievements. *Am J Pharmacogenomics* 2003; **3**: 361–370.
- 38 Pirazzoli A, Recchia G. Pharmacogenetics and pharmacogenomics: are they still promising? *Pharmacol Res* 2004; **49**: 357–361.