

WHAT PHARMACIST NEEDS TO KNOW ABOUT PHARMACOGENOMICS?

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ABSTRACT

Pharmacogenomics is an excellent example of continuing education way it is so important to pharmacist and other health professionals. As a promise in the future a disease could be ranked into genetic categories, allowing bespoke tailoring of medicine to maximize therapeutic effects and reduce the potential of an adverse drug response. In order to prepare academic pharmacy to respond to the impact of the emerging knowledge of genetics and genomics on the future roles of pharmacists, we discuss what pharmacist really needs to know about Pharmacogenomics. Briefly, here we describe: i) current known genetic variation that interact with therapies and needs to detect them; ii) how pharmacogenomics could change the practice of pharmacy; and iii) develop a series of "hot-topics" on basic competencies for pharmacist in terms of knowledge and skills. However, these features could be useful recommendations for the faculty to guide academic institutions and educational programs so they may prepare health professionals with the necessary abilities for their future practice.

Keywords: Pharmacogenomics, Health education, Genotypes, tests, knowledge base.

INTRODUCTION

Recently, advances in molecular biology and genetics have led to many changes in pharmaceutical sciences. In particular, with developments in pharmacogenetics and pharmacogenomics, detailed information about specific regions of the human genome is available and the genetic basis for disease and success/failure of pharmacotherapy is being studied¹.

All disciplines in the pharmacy curriculum will be affected to some degree by the increased understanding of the drug response through pharmacogenomics. Pharmacy institutions and practitioner organizations must play a central role in educating health professionals on how best to use the applications of advancing pharmacogenomic research, and in articulating the role of pharmacists and pharmaceutical scientists in the development and use of gene-based therapies, as well as in making treatment choices as a result of available patient-specific genetic information.

There are currently known genotypes that are used for the selection of personalized medications, and the number of important pharmacogenomic discoveries is increasing steadily. At present, these applications are limited largely to medications that have narrow therapeutic indices (e.g., anticancer medications), but as additional pharmacogenomic relationships are discovered, the number of applications will continue to grow².

Needs to detect genetic variations in Pharmacotherapy

Pharmacogenomic approaches have been applied to many existing therapeutic agents in an effort to identify relevant inherited variations that may better predict

patient response to treatment. Genetic variations which can alter the amino acid sequence of the encoded proteins, include nucleotide repeats, insertions, deletions, translocations and Single Nucleotide Polymorphism (SNPs). Such genetic polymorphisms in drug metabolizing enzymes like Cytochrome P450 family³, transporters like Multidrug Receptors-1⁴, and molecular targets have been actively explored with regard to functional changes in phenotype (altered expression levels and/or activity of the encoded proteins) and their contribution to variable drug response. The Table 1 describes some clinically relevant examples of genetic defects to illustrate the relevance of Pharmacogenomics in optimizing pharmacotherapy as a way to enhance efficacy and safety. For example a new generation of anticancer drugs have a high specificity towards tumour cells, providing a broader therapeutic window with less/low toxicity in comparison to conventional chemotherapies; therefore, these drugs represent a new and promising approach to targeted cancer therapy. These new drugs, are designed to interfere with a specific molecular target, usually a protein with a critical role in tumour growth or progression (i.e. tyrosine kinase). There are multiple types of targeted therapies available, including monoclonal antibodies, antisense inhibitors, and inhibitors of tyrosine kinase. Obviously, any of these new drugs sets up a selective pressure for tumour cells, which can survive and proliferate in its presence. The same basic principle seems to be true for protein kinase inhibitors; the best understanding of this problem at a molecular level comes from studies on imatinib resistance in Chronic Myelogenous Leukemia (CML) patients carrying BCR/ABL fusion gene. These imatinib-resistant clones, consisting in a single nucleotide mutation in ABL Kinase domain (with



consequent amino acid substitution), are successfully suppressed by second-generation of Tyrosine kinase inhibitors (i.e. Dasatinib, Nilotinib), still active on almost all imatinib-resistant mutants⁵.

Similarly to imatinib, two other biological drugs (Gefitinib and Erlotinib) showed a clinical activity in a subset of patients affected by Non Small Cell Lung Cancer (NSCLC). The mechanism of action of both of these is the selective

inhibition of kinase activity of Epidermal growth factor receptor (EGFR). Recently it has been reported in NSCLC patients that specific point mutation of EGFR gene in tumour cells select gefitinib responders patients (EGFR mutated), from non-responders (EGFR wild type)⁶. The availability of this kind of biomarkers could be a useful tool to understand an investigation of drug resistance.

Table 1: Most common known genetic abnormalities and their effect in pharmacotherapy

GENE ^a	Polymorphism (nucleotide translation)	Molecular effect	Drug	Effect on therapy
Cytochrome P450 family	Various Polymorphism	Decreased enzyme activity	Various	Inter-individual variability in Pharmacokinetics
TPMT2, 3A, 3C	Various Polymorphism	Rapid degradation	6-MP Thioguanine	Hematopoietic toxicity
UGT1A 28	TA repeats in 5' promoter	Low expression	Irinotecan	Neutropenia toxicity
MDR1	(C3435T)	Low expression	various	Drug resistance
TYMS	3 tandem repeats	High expression	5-FU, Metatrexate	Drug resistance
DHFR	T91C	Increased enzyme activity	Metatrexate	Drug resistance
MTHFR	(C677T)	Decreased enzyme activity	Metatrexate	Toxicity
c-KIT	(T1982C) (T81421A)	Constitutive signal activation	Imatinib	desensitizes activity in GIST
c-KIT	D816V	Unknow	Imatinib Semaxinib	Good response in t(8;21)-positive AML
EGFR	L858R	Unknow	Gefitinib Erlotinib	Good response in NSCLC
BCR/ABL fusion gene	t(9;22) BCR/ABL	Constitutive signal activation	Imatinib Dasatinib Nilotinib	Good response in CML
ABL	T315I M351T		Imatinib	Drug resistance
PML/RAR α fusion gene	t(15;17) PML/RAR α	Block of maturation of Myeloid cells	All Trans Retinoic acid (ATRA)	Good response in AML-M3 subtypes
ADRB1 ADRB2	R389G	G-protein altered	b-bloccants	desensitizes activity
MHC class B 1	Several SNPs including codon K751Q	HLA-B-5701 aploptype	Abacavir	hypersensitivity r
VKORC1	Many, VKORC1 haplotypes including codon G3673A	associated with a higher/low warfarin dose	Warfarin	Variable anticoagulant effect

Abbreviations: TPMT = thiopurine methyltransferase; UGT1A1 = UDP-glucuronosyltransferase 1A1; MDR1 = multidrug resistance 1; TYMS = thymidylate synthase; DHFR= Dihydrofolate reductase; MTHFR = 5,10-methylene tetra hydrofolate reductase; EGFR= Epidermal Grow Factor Receptor; 5-FU = 5-fluorouracil; 6-MP = 6-mercaptopurine; AML= Acute Myeloid Leukemia; NSCLC= Non-Small Cell Lung Cancer; CML= Chronic Myeloid Leukemia; ADRB: adrenergic b-receptors; VKORC1: Vitamin K epoxide reductase Complex 1;

The present list is not meant to be comprehensive.

^a Genes are available for genotyping test or under consideration for clinical diagnostics.



Table 2: Basic competencies (in terms of knowledge and skills) in Pharmacogenomics for pharmacist.

	Knowledge	Skills
Genetics	<ul style="list-style-type: none"> ▪ Basic concepts ▪ Nomenclature ▪ Most recently SNPs causing intervariability respons to drugs ▪ the role of genetic factors in preventing disease ▪ the difference between clinical diagnosis of disease and identification of genetic predisposition ▪ genomic tests available in specialized laboratories 	<ul style="list-style-type: none"> ▪ current information about pharmacogenomics for self, clients and colleagues ▪ Explain basic concepts of probabilities of genetic factors in maintenance of health and development of disease ▪ seek coordination and collaboration with an interdisciplinary team of health professionals ▪ identify patients who have undergone pharmacogenetic testing in the past so that a specific test is not repeated unnecessarily
Drug Research and development	<ul style="list-style-type: none"> • Know where/how to find information about Pharmacogenomics. • Recognize data about proteins that influence drug respons. • understand how association between genomic variation and drug response are investigate and uncovered • understand that pharmacogenetic testing is like all other clinical testing - it will not have 100 percent reliability, but rather is used along with other clinical information 	<ul style="list-style-type: none"> • critically evaluate information obtained from pharmacogenetic/genomic clinical trials and identify limitations in study design, technology, and data interpretation that will influence patient care • identify the epidemiologic implications of pharmacogenetic/genomic studies and its impact at the societal level as well as that of the individual patient • interpret the results of pharmacogenetic testing, and make drug therapy recommendations based on the results • -identify drug therapy problems that may be related to genetic variability, even when a pharmacogenetic test has not been done
Ethical, social and economics implications	<ul style="list-style-type: none"> ▪ understand the potential physical and/or psychosocial benefits, limitations, and risks of pharmacogenetic information for individuals, family members, and communities ▪ appreciate the ethical, legal and social issues related to pharmacogenetic testing and recording of genetic information (e.g., privacy, the potential for genetic discrimination in health insurance and employment) ▪ understand the increased liability that accompanies access to detailed patient information ▪ maintain the confidentiality and security of patient health records 	<ul style="list-style-type: none"> ▪ discuss costs of pharmacogenetic services, benefits and potential risks of using health insurance for payment of pharmacogenetic services, including potential risks of discrimination. ▪ tailor information and services to patient culture, education, and language ▪ adopt a code of conduct in patient treatment that is free of racial, ethnic, and religious bias ▪ identify appropriate resources offered by professional organizations, disciplines, or institutions

How pharmacogenomics could change the practice of Pharmacist? New responsibilities for the pharmacist who is required to interpret and preserve the genomic profile of his patients.

Pharmacogenomics has the potential to provide patient's data upon which the selection of drugs and doses can be

individualized and optimized. The exciting prospect is for pharmacogenomics is to yield a powerful set of molecular diagnostics that will become routine tools by which pharmacists and physicians select the best individual medications and doses, instead of starting patients on the "average dose" that was found to be safe and effective in most patients in large clinical trials. For example, unlike,



serum creatinine to measure renal function, or serum transaminase to assess liver function, or essentially all other biochemical tests, a patient's genomic profile only needs to be determined once because its data not change over time. Using the amount of genomic DNA that can be isolated from just few milliliters of blood, it is possible to detect thousands of gene, even with current technology, like DNA microarrays, or so called "DNA chips"⁷. So, taken together, the process will be to collect a single blood sample from each patient, submit an aliquot of the sample to a reference laboratory for analysis of a genotyping panel, and test for those established to be important determinants of drug disposition and effects. The results of this screening tests would be electronically deposited into a secured database, into and out of which data can be accessed only with The patient's authorization (to her/his pharmacists, physicians, other health care professionals). The results of these tests will not be simply a list of gene SNPs, but rather a report formatted and interpreted according to the patient's diagnosis and treatment options. For example, the report could be a recommended protocol for the selection of anticoagulation drugs, starting with those most likely to be effective and well tolerated, based on the patient's genotypes for the panel of genes known to be significant determinants of the disposition and effects of coagulation medications (i.e. VKORC1 mutation and warfarin). As patients experience additional illnesses, additional genotypes will be characterized and the data added to the same secured database, to which the physicians and pharmacists would be granted access they need to make treatment decisions for the patient's future. Of course, these new tools will not replace the more conventional biochemical tests that are now routinely used to assess organ function and disease progression, rather they will complement these contemporary tests and provide additional tools for selecting medications and dose that are optimal for each patient. Furthermore, genotyping will not obviate the need to follow up assessment of response, adherence to treatment, or drug interactions, which will continue to be important clinical responsibilities for pharmacists.

Outlook and current opinions

Today, pharmacist assist physician by checking items listed on a prescription for possible interaction between drugs; tomorrow's pharmacist could conceivably interpret genetic profile and genetic test. Core competence now serves as the dominant framework for the education of health professionals, replacing a centuries-old model of knowledge-based learning and testing. This new imperative requires that health professionals master not only the knowledge base of their discipline, but also that they understand why, when, and how that knowledge should be applied to improve health outcomes for their patients⁸. We believes it is essential that pharmacist and organizations responsible for training and teaching health professionals, adopt guidelines competencies and integrate genetics content into ongoing education.

Current opinion on basically competencies of the pharmacists and health professions includes knowledge and skills (tab. 2), on three fundamental features: i) genetics of disease, allowing understand how identification of disease associated genetic variations facilitates development of preventions and therapies ; ii) pharmaceutical research and drugs developments, allowing to understand how therapy protocols are ranked into patient's genetic profile, and way the company influence the development of new drugs⁹; iii) ethical-social-economical implications is fundamental to identify the factors that might contribute to a successful integration of pharmacogenomics into international health and public policy¹⁰.

Finally, pharmacogenomics will make the practice of pharmacy and medicine less an art and more a science, thereby improving the efficacy and reducing the toxicity that result from therapy.

Appendix to table 2

Issues listed in table 2, derives in part, from, National Coalition for Health Professional Education in Genetics¹¹ and in part from, databases available to the genetic community with a wide range of aims and scopes including: i) those presenting guidelines on pharmacogenomics related to government policy such as Food and drug Administration FDA (www.fda.gov/cder/genomics/default.htm) and European Medicine Agency EMEA (www.emea.europa.eu/pdfs/human/ich/43798606en.pdf); ii) those provide a genetic row data such as Genbank (www.ncbi.nlm.nih.gov/Genbank/index.html); and iii) those providing higher level structure and annotation such as Pfam (www.sanger.ac.uk/Software/Pfam). Other types of large-scale data resource used in Pharmacogenetic testing include publication databases, gene-drug pathway such as Pharmacogenomics Knowledge Base (www.pharmgkb.org/index.jsp) and disease/gene information resources and tools such as OMIM (www.ncbi.nlm.nih.gov/sites/entrez?db=omim/) or Orphanet. (www.orpha.net). Clearly there are overlaps between many of these database and an attempt at categorize them to any detailed degree may be difficult and unproductive.

(all world web site has been accessed until 20th june 2010)

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