WHAT HEALTH PROFESSIONS IN ONCOLOGY NEEDS TO KNOW ABOUT PHARMACOGENOMICS?

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ABSTRACT - Background: Pharmacogenomic offers the promise to ranking an oncologic disease into genetic sub-categories, allowing bespoke tailoring of medicine to maximize therapeutic effects and to reduce adverse drug response. This new feature requires for health professionals to have competencies not only for their discipline, but also for the skills on why, when, and how that pharmacogenomic knowledge should be applied to improve personalized therapies for their patients. Current opinion on basic competences of health professions includes knowledge and skills on two fundamental features: a) genetics of disease, to allow the understanding and the identification of diseases associated to genetic variations, and to facilitate the application of new genomic tests; and b) ethical, social and economical implications that are fundamental to identify those factors that might contribute to a successful integration of pharmacogenomics into international health and public policy.

AIM: Briefly, we described i) current knowledge on genetic variations that interact with therapies, the need to detect them with the most common available methods; and ii) ethical, social and economic issues related to pharmacogenomic testing and recording of genetic information (e.g., critical evaluation of the development of new tests, privacy, the current absence of public reimbursement, etc.).

Conclusions: In conclusion, these issues should be useful recommendations for academic institutions and educational programs to prepare health professionals in pharmacogenomic field with the necessary abilities for their future practice.

Keywords: Pharmacogenomics, Health profession education, Genotyping services laboratory, Genetic knowledge base, Cost-effectiveness.

INTRODUCTION

The developments in pharmacogenetics and pharmacogenomics (PGx), detailed information about human genome made available and the genetic basis for success/failure of pharmacotherapy in oncology have being studied¹. Pharmacogenetic knowledge is rapidly developing and changing; it is imperative that healthcare professionals keep abreast of advances and
clinical indications. The current knowledge of health professions regarding PGx is still low. There exists an acute lack of education of both physicians and pharmacists regarding pharmacogenetics and personalized care\(^2\). Academic curricula are slowly including teaching of this field in their courses. Healthy institutions and academic organizations must play a central role in educating health professionals on the best use for applications of advancing pharmacogenomics research applied to oncology, and in articulating on the role of physicians and pharmacists in the development and use of gene-based therapies, as well as in making treatment choices as the result of available patient-specific genetic information\(^3\).

The large number of drug options also means that physicians are often spoilt for choice, and have a low threshold to consider alternative therapies when toxicity becomes unmanageable. However, it is often forgotten that genetic testing is not only predictive for treatment related toxicity or allows for dose adjustment, but also determines response or lack thereof. It is frequently imperative that must be done before treatment, as giving inappropriate treatment may result in an outcome poorer than the alternative\(^1\). A ‘treat-and-see’ approach has ethical and legal implications in this era where genetic testing is readily available. It delays and even potentially deprives patients of appropriate treatment, and deterioration is often rapid without it. Moreover, we think that genetic testing could have a key role for the treatment choice in the so called frail patients (i.e. elderly and HIV-positive patients) for whom the efficacy and especially the toxicity profile are important aspects\(^4,5\).

However, one should keep in consideration that it will not be feasible to conduct randomized trials on each and every diagnostic test, and the economic value of such tests can be modelled using decision analysis techniques.

The goal of this review is to provide information (in terms of knowledge-base in genetics, ethical, social and economic) for the health profession about the genetic variations implicate in oncologic pharmacotherapy.

### Table 1. Most Significant Genetic Variants in Oncology and Their Effect in Pharmacotherapy

<table>
<thead>
<tr>
<th>Gene</th>
<th>Polymorphism (nucleotide translation)</th>
<th>Molecular effect</th>
<th>Drug</th>
<th>Effect on therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytchrome P450 family</td>
<td>Various</td>
<td>Decreased enzyme activity</td>
<td>Various</td>
<td>Inter-individual variability in Pharmacokinetics</td>
</tr>
<tr>
<td>TPMT, 3A, 3C</td>
<td>Various</td>
<td>Decreased enzyme activity</td>
<td>6-MP</td>
<td>Hematopoietic toxicity</td>
</tr>
<tr>
<td>UGTIA 28</td>
<td>7A repeats in 5' promoter</td>
<td>Decreased enzyme activity</td>
<td>Irinotecan</td>
<td>Neutropenia toxicity</td>
</tr>
<tr>
<td>MDR1</td>
<td>(C3435T)</td>
<td>Low expression</td>
<td>Various</td>
<td>Drug resistance</td>
</tr>
<tr>
<td>FYMS</td>
<td>3 tandem repeats</td>
<td>Increased enzyme activity</td>
<td>5-FU, Metotrexate</td>
<td>Drug resistance</td>
</tr>
<tr>
<td>DPYD</td>
<td>IF514G</td>
<td>Decreased enzyme activity</td>
<td>5-FU, Metotrexate</td>
<td>Neutropenia toxicity</td>
</tr>
<tr>
<td>DHFR</td>
<td>T91C</td>
<td>Decreased enzyme activity</td>
<td>Methotrexate</td>
<td>Drug resistance</td>
</tr>
<tr>
<td>MTHFR</td>
<td>C677T (A1298C)</td>
<td>Decreased enzyme activity</td>
<td>5-FU, Metotrexate</td>
<td>Toxicity</td>
</tr>
<tr>
<td>c-KIT</td>
<td>D560</td>
<td>Constitutive signal activation</td>
<td>Imatinitib</td>
<td>Desensitizes activity in GIST</td>
</tr>
<tr>
<td>N267K</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>K-RAS</td>
<td>G12x</td>
<td>Inhibition of the Tyrosine Kinase</td>
<td>Cetuximab</td>
<td>Desensitizes activity in colon-rectum carcinoma</td>
</tr>
<tr>
<td>G13D</td>
<td>Kinase domain-binding drug</td>
<td>Panitumomab</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B-RAF</td>
<td>V600E</td>
<td>Kinase domain-binding drug</td>
<td>Vemurafenib</td>
<td>Good response in melanomas</td>
</tr>
<tr>
<td>EGFR</td>
<td>L858R</td>
<td>Inhibition of the Tyrosine Kinase</td>
<td>Gefitinib</td>
<td>Good response in NSCLC</td>
</tr>
<tr>
<td>BCR/ABL fusion gene</td>
<td>t(9;22)</td>
<td>Constitutive signal activation</td>
<td>Imatinib</td>
<td>Good response in CML</td>
</tr>
<tr>
<td></td>
<td>BCR/ABL</td>
<td></td>
<td>Dasatinib</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Nilotinib</td>
<td></td>
</tr>
<tr>
<td>ABL</td>
<td>T315I, M351T</td>
<td>Inhibition of the Tyrosine Kinase</td>
<td>Imatinib</td>
<td>Drug resistance in CML</td>
</tr>
<tr>
<td></td>
<td>fusion gene</td>
<td></td>
<td>Dasatinib</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Nilotinib</td>
<td></td>
</tr>
<tr>
<td>PML/RARA fusion gene</td>
<td>t(15;17)</td>
<td>Block of Myeloid lineage cells</td>
<td>All Trans Retinoic acid (ATRA)</td>
<td>Good response in AML-M3 subtype</td>
</tr>
</tbody>
</table>

Abbreviations: TPMT = thiopurine methyltransferase; UGT1A1 = UDP-glucuronosyltransferase 1A1; MDR1 = multidrug resistance 1; TYMS = thymidylate synthase; DPYD = Dihydropyrimidine Deaminase; DHFR = Dihydrofolate reductase; MTHFR = 5,10-methylene tetrahydrofolate 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; PML = Acute Promyelocytic Leukemia; The present list is not meant to be whole comprehensive.

*Genes are available for genotyping test or under consideration for clinical diagnostics
GENETICS COMPETENCIES

Pharmacogenomic approaches have been applied to many existing therapeutic agents in an effort to identify relevant inherited variations that may better predict patients’ response to treatment. Genetic variations, which can alter the protein expressions and/or amino acid sequence of the encoded proteins, include nucleotide repeats, insertions, deletions, translocations and Single Nucleotide Polymorphisms (SNPs).

Such genetic polymorphisms in drug metabolizing enzymes like the Cytochrome P450 family; transporters like Multidrugs Receptors-1; 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 following Table 1 describes some clinically relevant examples of genetic defects illustrating the relevance of PGx in optimizing pharmacotherapy, as a way to enhance efficacy and safety. For example the new generation of anticancer drugs have high specificity toward tumour cells, provide a broader therapeutic window with less/toxicity in comparison with 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, many of these new drugs set up a selective pressure for tumour cells that 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 Leukaemia (CML) patients carrying BCR/ABL fusion gene. These imatinib-resistant clones, consisting a single nucleotide mutation in ABL Kinase domain (with consequent amino acid substitution), are successfully suppressed by second-generation Tyrosine kinase inhibitors (i.e. Dasatinib, Nilotinib), still active on almost all imatinib-resistant mutants.

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

GENOTYPING METHODS AND ECONOMICS COMPETENCIES

The technology platform needed for genotyping is different; it does depend from type of mutation, acquired genetic change, or the analysis of inherited SNPs. No single genotyping platform stands out as ideal and rational selection of the best methods to detect them is dependent from the specifics aims of different laboratories. Furthermore, the most popular technologies currently used in specialized laboratories, focus on the transition from research setting to clinical laboratory as previously discussed by other authors.

As genomics-based technologies are widely introduced in clinical laboratories testing setting, the risks of mishandling or misinterpreting data from patient’s sample analyses becomes a significant consideration with especially dramatic consequences where the test becomes commercially available to the public.

Generally, genotyping is performed either by custom clinical laboratories or academic referenced laboratories, as well as by using commercial kits (when available). In the USA, diagnostics products are regulated by the Food and Drug Administration (FDA), whereas diagnostic services are under the rules of the Clinical Laboratory Improvement Act (CLIA). In Europe this field is covered by in vitro Diagnostic (IVD) directive, without a distinction between commercial products (used by laboratories) and diagnostics service. In both circumstance, a voluntary list of international laboratories (with CLIA certification in the US and CE mark in Europe) that perform genetic tests can be found on the National Institute of Health-funded website named GeneTests™ [http://www.ncbi.nlm.nih.gov/sites/GeneTests/lab?db=GeneTests], although only a small minority of genetic tests listed on this site are PGx tests. Clinical laboratories may develop and validate tests in-house (“home-brew”) and perform them as a laboratory service; which may further reduce the cost of analysis. Furthermore, laboratory-developed molecular tests are in contrast with patented kit manufactured by company biotech. The impact of these commercial controversial was low studied by Academic Institution, except for the positive model of the US Department of Health and Human Services (HSS) [http://oba.od.nih.gov/SACGHS/]. In the field of oncology, there are new 38 genomic tests approved by FDA since 2006.
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gained 17. However, we still need a precise demon-
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routinely incorporated either into clinical practice or
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pharmaceutical companies should be involved with the initial development of
PGx assays because they have the primary data and
information necessary for this stage of assay develop-
ment. However, this assay development activity
should be transferred to outside referenced labora-
tories, clinical core laboratories in academic health
centers, or established Clinical Research Organiza-
tions when research and development transit into
clinical application because these independent ex-
ternal sites are able to handle this function16.

Drug selection based on genetic assessment
may be considered confidential information. Cur-
rently, PGx testing may provide detailed genetic
information necessary for health professions to
prescribe the correct drug and its dose. The skills
of health operator must be orientated to maintain
the confidentiality and security of patient’s health
records. In this field, the clinical laboratories could
be the most proficient means to protect
patient/physician confidentiality.

Reimbursement or payment for genetic testing is
another topic of considerable consequence that is al-
ready creating controversy among health mainte-
nance organizations, healthcare providers, and the
patients themselves. One can predict, however, that
health insurance companies will be very interested in
patient PGx testing to document the proper dosing of
expensive prescription drugs and hence reduce the
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stration that PGx tests offer an added value, in terms of
relative cost and benefit.

Furthermore, trials evaluating the pharma-
coeconomic impact of genotyping testing before
therapy will likely provide answers for policy mak-
ing in the merging of PGx testing into clinical
practice. The primary aim of a cost-effectiveness
analysis is to provide sufficiently robust informa-
tion for decision-makers to allocate resources to
healthcare interventions. Overviews of cost-effec-
tiveness studies on PGx technologies are now
available17. A relevant example is the National In-
institute for Health and Clinical Excellence (NICE).
NICE forms a Diagnostic Advisory committee, which is
will be interested in
pharmaceutical companies, especially if inadequate
testing excludes some patients who might benefit
without charging or, conversely, long-term
dosing continues with a treatment that does not have
good clinical efficacy15. Pharmaceutical companies
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CONCLUSION AND FUTURE OUTLOOK

The potential is enormous for pharmacogenomics
to yield a powerful set of molecular diagnostics that
will become routine tools by which pharmacists and
physicians select the proper medications and
doses for each individual patient. Instead of starting
patients on the “average dose” that was found to be
safe and effective in most patients in large clinical
trials, pharmacogenomics has the potential to pro-
vide patient-specific data upon which the selection of
drugs and doses can be individualized and opti-
mized. Using the amount of DNA that can be iso-
lated from just few milliliters of blood, it is possible
to determine thousands of genotypes in diverse
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an aliquot of the sample to a reference
laboratory for analysis of a panel of genotypes, and
for those established to be important determi-
nants of drug disposition and effects. The results of
this specific panel of genetic variants would be
electronically deposited into a secured database,
and out of which data can be accessed only
with the patient’s authorization (to her/his 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 algorithm for selecting antineoplastic medications, 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 chemotherapeutic medications (i.e. DPYD mutation and 5-Fluorouracil administration). As patients experience additional illnesses, additional genotypes will be characterized and the data added to the same secured database, to which the patient’s future physicians and pharmacists would be granted access as needed to make treatment decisions. Of course, pharmacogenomic testing is like all other clinical testing; it will not have 100 percent reliability, but rather is used along with other clinical information.

Appendix to table 2: Issues listed in table 2, derives in part, from, National Coalition for Health Professional Education in Genetics (www.wikigenetics.org/index.php/NCHPEG-Principles_of_Genetics_for_Health_Professionals) 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 (www.fda.gov/cder/genomics/default.htm) and European Medicine Agency (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 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). The table lists of FDA-approved drugs with pharmacogenomic information in their labels are available at www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm. Clearly there are overlaps between many of these database and an attempt at categorize them to any detailed degree may be difficult and unproductive. Website accessing: until February 2014

TABLE 2: BASIC COMPETENCIES (IN TERMS OF KNOWLEDGE AND SKILLS) IN PHARMACOGENOMICS FOR HEALTH PROFESSION.
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