

## Challenges and Pitfalls in the Introduction of Pharmacogenetics for Cancer

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### Abstract

There have been several success stories in the field of pharmacogenetics in recent years, including the analysis of HER2 amplification for trastuzumab selection in breast cancer and VKORC1 genotyping for warfarin dosing in thrombosis. Encouraging results from these studies suggest that genetic factors may indeed be important determinants of drug response and toxicity for at least some drugs. However, to apply pharmacogenetics appropriately, a thorough understanding of the scope and limitations of this field is required. The challenges include an appreciation of biological variability, logistical issues pertaining to the proper management of information, the need for robust methods and adequate sample quality with well-designed workflows. At the same time, the economics of pharmacogenetic testing from the perspective of clinicians, patients, governments, insurance companies and pharmaceutical companies will play an important role in determining its future use. Ethical considerations such as informed consent and patient privacy, as well as the role of regulatory bodies in addressing these issues, must be fully understood. Only once these issues are properly dealt with can the full benefits of pharmacogenetics begin to be realised.

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### Introduction

Pharmacogenetics, by definition, refers to the study of genetic differences in metabolic pathways which can affect an individual's responses to drugs in terms of both therapeutic and adverse effects.<sup>1</sup> In recent years, there have been several success stories such as HER2 for trastuzumab in breast cancer and VKORC1/CYP2C9 for warfarin in thrombosis.<sup>2-6</sup> Encouraging results from these studies suggest that genetic factors may indeed be the major determinants of drug response for at least some drugs. This presents the possibility of personalising treatments in the near future to better suit individual patients. By stratifying patients according to their genetic profile, the aim is to identify those that will benefit from available treatments in terms of maximum response and minimal toxicity. However, as with 'conventional' disease-genetic testing, a

high level of expertise is required to perform these tests and to interpret the results correctly.<sup>7</sup> Thus, it is important to be aware of the numerous pitfalls regarding biological agents, logistics and ethical issues that must be overcome before the benefits of personalised medicine can be realised. In addition to the scientific aspects, the economic challenges associated with the introduction of pharmacogenetic tests should also be considered.

Pharmacogenetic markers often suffer the same fate as the attrition observed during drug development. Starting with thousands of potential candidates, companies are often left with just one or a small number of viable pharmacogenetic markers after many years of research and millions of dollars invested. In particular, given that Food and Drug Administration (FDA) are beginning to request that 'marker-

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negative' patients be included in Phase III trials with a view to potential off-label use, further delays can be expected in the routine introduction of pharmacogenetic markers.

Another common barrier to the successful implementation of pharmacogenetic markers is the lack of reproducibility in the reported results. One example is the CETP Taq-I variant and response to statins in coronary heart disease. Despite the initially promising results observed in association studies, the relationship failed the test of replication in larger studies.<sup>8</sup> Similarly, a recent large-scale clinical trial that investigated pharmacogenetic markers of adverse events and response to chemotherapy in metastatic colorectal cancer failed to validate most previously reported genotype-toxicity or -efficacy associations. This was attributed to logistic issues such as differences in chemotherapy dosing or scheduling, but more importantly to the fact that many previously identified markers were likely to be false positives resulting from multiple comparisons and non-representative samples.<sup>9</sup> It also highlights the importance of distinguishing between statistically significant and biologically/clinically significant. For instance, an odds ratio of 1.5 may be statistically significant, but can hardly be considered clinically relevant. A recent study of published meta-analyses and HuGENet reviews of gene-disease associations concluded that the amount of scientific evidence was insufficient to support useful applications for most of the associations reported to date.<sup>10</sup>

The difficulties mentioned above have thus far prevented the implementation of routine pharmacogenetic testing for all but a handful of applications. It is important to be equipped with sufficient knowledge of the limitations and difficulties involved in pharmacogenetic testing. In this review, we highlight some of the common pitfalls in pharmacogenetics in terms of biological, logistic, cost and ethical issues.

## Biological Issues

Several important factors contribute to biological variability. One key issue is gene penetrance, referring to the proportion of individuals who express a trait or phenotype out of those that carry a particular associated allele or genotype. Penetrance should be considered concurrently with other factors such as allele and genotype frequencies. For example, some genes such as *BRCA1* have a high penetrance but a low variant frequency.<sup>11,12</sup> Conversely, other genetic variants have a low penetrance but a relatively high frequency, and may have as much an attributable risk as *BRCA1*.

The number of variants to be tested is another consideration. One should be aware that the phenotype of interest is unlikely to be attributable to any single gene or

variant, in particular for a complex disease such as cancer. An example is the *DPYD* exon 14 skipping variant which was found to explain only about 15% of observed 5-FU toxicity.<sup>13,14</sup> In deciding upon the panel of variants to be used in a pharmacogenetic diagnostic test, one often has to decide between a more complete panel or one that includes only the most common variants. For example, although 11 variant alleles have been associated with low TPMT enzymatic activity, over 95% of inherited TPMT deficiencies are due to the 3 most common alleles.<sup>15,16</sup> By incorporating the additional variants, it is possible to explain the remaining 5%. Although it is now feasible to sequence all possible variants using high-throughput arrays, the most efficient use of limited sample must also be considered given the marginal improvement in prediction.

Various statistical measures of assay performance including sensitivity and specificity are important for decision-making. In breast and prostate cancers, a multigenic approach consisting of genotype combinations was able to predict risk with greater sensitivity than single genotypes.<sup>17,18</sup> At the same time, there are likely to be other gene-environment interactions involving lifestyle and diet that could play a role but are impossible to control in the usual setting of an association study. The possibility that candidate genetic variants may be associated with baseline characteristic of the study population such as gender should be considered and interpreted with caution.<sup>14</sup>

To understand the appropriate application of pharmacogenetic markers, a number of important issues need to be highlighted. One is the difference between germline and somatic variation. Germline variations, consisting mainly of single nucleotide polymorphisms and copy number variations, are found in cells throughout the body and are therefore more likely to be related to host issues such as toxicity. Somatic changes, such as gene mutations, structural variations and methylation that occur only in the tumour cells are more likely to be associated with tumour response. Although the majority of current applications in pharmacogenetics are germline variations that affect metabolism, more emphasis on somatic changes are expected as these play a large role in determining response, particularly for the targeted agents including kinase inhibitors.<sup>19</sup>

Another difference to take note of is that of a prognostic marker versus a predictive marker. By definition, prognostic biomarkers provide information about the patients overall outcome from disease, regardless of therapy. A predictive biomarker on the other hand provides information about the likely effect of a therapeutic intervention.<sup>20</sup> It is important to avoid confusing the two terms as this can lead to incorrect conclusions, particularly if the wrong treatment groups are compared and if trials are not designed to test the

corresponding hypotheses.

### Logistic Issues

The importance of proper management of information, appropriate methods and samples, as well as carefully designed workflows cannot be emphasized enough. This is highlighted by the recent suspension of 3 personalised medicine clinical trials.<sup>21</sup> The trials were based upon a publication in *Nature Medicine* in which the authors claimed that signatures derived from gene expression data could be used to direct the most suitable chemotherapy for cancer patients.<sup>22</sup> The trials were initially suspended following the report by 2 biostatisticians of an inability to replicate several findings in the original article. Investigation of additional studies revealed that simple errors such as misalignment of data in rows or columns and the mix up of group labels had occurred.<sup>23</sup> This serves to highlight the importance of highly competent infrastructure for analysis, as seemingly minor mistakes can have serious repercussions in which patients are allocated to sub-optimal or even harmful treatment arms.

Selection of the most appropriate and accurate detection method is another major consideration. Concordance in the immunohistochemical results obtained using different antibodies, fluorescence in situ hybridization (FISH) and other methods has been widely investigated for HER2 testing in relation to the appropriate treatment of breast cancer.<sup>24–26</sup> Given the importance of *KRAS* mutation status in the selection of appropriate therapy for advanced colorectal cancer patients, a recent multicenter blinded comparison revealed that comparable results were obtained using a variety of different assay platforms. Concordance values of 83% and 96% were obtained for *KRAS* mutation status in samples of frozen and paraffin tissues, respectively.<sup>27</sup> This study nevertheless reported differences in reagent costs, labour and turnaround time, detection limit and availability of sequence outputs between the different methods.<sup>27</sup>

Sample heterogeneity is an area of logistics that needs to be addressed for clinical application. In many studies, high-throughput assays such as gene expression and methylation arrays are often used to identify candidate pharmacogenetic markers. However, unlike cell lines, clinical tumour samples have heterogeneous cell content. In a recent study using Illumina Goldengate methylation arrays involving 98 pairs of gastric tumours and matching normal tissues, we demonstrated that tumour cell content significantly influenced the interpretation of apparent methylation levels and hence of candidate gene identification.<sup>28</sup> Without taking tumour heterogeneity into account, one runs the risk of inaccurately identifying potential pharmacogenetic markers.

As mentioned earlier, novel and efficient workflows are essential for successful clinical integration. Following

discussion between scientists and clinicians on testing for epidermal growth factor receptor mutation in the care of lung cancer patients, it was apparent that the length of time to receive test results was of primary concern.<sup>29</sup> Clinicians are unlikely to consider using molecular genetic tests unless the results can be delivered within a reasonable timeframe.

Similarly, a survey of clinicians in 4 European countries indicated that the quality of technical infrastructure including the convenience of sending samples and direct communication with the laboratory would affect the clinical uptake of molecular tests.<sup>30</sup> The lack of standard protocols for processing samples for genetic tests was also identified as a significant barrier to successful implementation.<sup>31</sup> Experience suggests that with proper planning in place before the commencing of a trial, a high compliance rate can be achieved. This was seen for example in the BATTLE (Biomarker-integrated Approaches of Targeted Therapy for Lung cancer Elimination) trial where the goal was to profile lung tumours with the aim of developing personalised therapy. Using a novel clinical trial design and tissue collection procedures, a compliance rate of close to 80% was obtained for the challenging task of obtaining 3 core biopsies per tumour.<sup>32,33</sup>

As with the development of any diagnostic test, pharmacogenetic tests need to be rigorously evaluated for various aspects such as sensitivity, specificity and positive predictive value (PPV). Since sensitivity and specificity are not fully informative regarding the correct test result, PPV is often used. However, it is important to realise that PPV is highly dependent on the phenotype prevalence. Consequently, PPV may not be directly transferable between different populations or ethnic groups where the underlying phenotype frequencies may differ.<sup>34</sup> As mentioned earlier, differences in the frequency of genetic variants between different ethnic groups could also impact on the interpretation of gene penetrance.<sup>35,36</sup> Since the results of pharmacogenetic tests can have serious repercussions for patients, the reliability of the assays is of utmost importance.

### Economic Issues

The economics of pharmacogenetic testing from the perspective of both clinicians and pharmaceutical companies will play an important role in determining its introduction for routine application. Although several studies have previously reported on the cost-effectiveness of HER2 and TPMT testing,<sup>37,38</sup> funding remains a major issue for physicians in Europe.<sup>30</sup> Apart from the direct cost of the test itself, indirect costs such as genetic counselling and additional visits to the clinic also need to be considered.<sup>39</sup> For example, up to 78% of individuals who considered using genetic testing services would ask for help from their

physician to interpret the results, thus leading to increased costs and pressure on the healthcare system.<sup>40</sup>

To encourage the routine use of pharmacogenetic testing in a clinical setting, much needs to be done to convince both private insurers and government healthcare providers to cover the associated costs. Without this support, doctors are unlikely to order such tests on a routine basis in light of the additional financial burden for their patients. For example, TPMT testing is not routinely carried in the Netherlands because reimbursement costs have yet to be arranged.<sup>30</sup>

From the standpoint of pharmaceutical companies, the development of pharmacogenetic markers is an expensive and risky process. The majority of companies are currently using biomarkers to facilitate their research and most have programs in place for companion diagnostics. The majority of executives from top biopharmaceutical companies have indicated they are developing biomarkers for almost half their compounds, but less than 10% have plans to launch companion diagnostic tests within the next 5 to 10 years.<sup>41</sup> This is due mainly to the incursion of additional time and cost at a time of increasingly strict demands from regulatory bodies. Based on a hypothetical model, start-up molecular diagnostic companies are likely to experience decreases in profit amounting to millions of dollars with just a single year of delay in FDA approval.<sup>41</sup>

## Ethical Issues

Several ethical issues need to be addressed before pharmacogenetic tests can be applied in a routine clinical setting. These include informed consent, use and storage of genetic information, confidentiality, pre- and post-test counselling, as well as discrimination and stigmatization of groups and individuals.<sup>7,42,43</sup>

Informed consent from the patient may not provide complete protection of their rights. There has been some evidence that patients who participate in clinical trials often do not fully understand the details of trial procedures and the potential risks. As such, their consent to participate in trials involving pharmacogenetic testing may not represent a truly informed decision.<sup>44</sup> Patients in such studies are often asked to give consent to the main clinical drug trial and testing involving the specified pharmacogenetics-drug effect. However, they are also often requested to give a general consent for unspecified genetic tests to be used in future pharmacogenetics research. Unaware to most of them, the patients are thus essentially giving permission to indefinitely use and store their genetic profiles for association with other personal information such as medical history.<sup>7,44</sup>

By prescribing the treatment for a patient according to his or her genotype derived from genetic testing, the indirect consequence is disclosure of that patient's genetic profile

at the medical and administrative level. Confidentiality is not possible in this case unless the patient declines the more suitable treatment for them.<sup>45</sup>

For pre- and post-test counselling, a high level of expertise is necessary to allow correct interpretation of the results.<sup>7</sup> The majority of patients have indicated they are likely to turn to their physician for help.<sup>40</sup> This not only increases the burden on clinicians but could also lead to incorrect conclusions and misleading interpretations. A previous survey found that of 407 physicians claiming to have attended courses or training on HER2 testing, 20% still found it difficult to correctly interpret test results.<sup>30</sup>

A direct impact of the possible discrimination of individuals according to their germline pharmacogenetic profile will be on insurance risk. The likelihood of a patient responding to treatment becomes an additional consideration to disease susceptibility when assessing an individual's insurance risk.<sup>45</sup> This information may be used by insurance companies to restrict enrolment for plans or to adjust the premiums accordingly.

## Conclusion

Despite the numerous challenges and pitfalls covered in this review, the future of pharmacogenetics remains promising. The potential benefits to be gained from the appropriate use of pharmacogenetic information are still being realised. Stratifying patients to receive the optimal treatments available promises to lead to considerable benefits in terms of improved quality of life, longer survival and cost savings.

Nonetheless, it is important to be aware that many obstacles remain. The clinical application of pharmacogenetic tests that lack a high level of accuracy carries the risk of over- or under-dosing patients. Currently, many clinicians are not equipped with sufficient background knowledge of pharmacogenetic testing and its limitations, thus possibly resulting in wrong treatment decisions.<sup>46</sup>

Regulatory bodies play a critical role in sanctioning the proper application of pharmacogenetic tests and several measures are currently in place to support this. Examples include the Proposed International Guidelines on Ethical Issues in Medical Genetics and Genetic Services by the World Health Organization (WHO) which mandates autonomy, beneficence and justice.<sup>45,47,48</sup> Another is the Genetic Information Nondiscrimination Act (GINA) passed through US Congress in 2008 that protects Americans from discrimination in terms of health insurance and employment opportunities based on genetic information. Finally, the long-awaited guidance document by the FDA on the development of companion diagnostics is likely to be launched during 2011. Given the recent advances in scientific knowledge

and technical capacity, pharmacogenetics can be expected to gain increasing prominence as clinical practice evolves towards personalised medicine and treatment.

## REFERENCES

- Klotz U. The role of pharmacogenetics in the metabolism of antiepileptic drugs: pharmacokinetic and therapeutic implications. *Clin Pharmacokinet* 2007;46:271-9.
- Burstein HJ, Harris LN, Marcom PK, Lambert-Falls R, Havlin K, Overmoyer B, et al. Trastuzumab and vinorelbine as first-line therapy for HER2-overexpressing metastatic breast cancer: multicenter phase II trial with clinical outcomes, analysis of serum tumor markers as predictive factors, and cardiac surveillance algorithm. *J Clin Oncol* 2003;21:2889-95.
- Sconce EA, Khan TI, Wynne HA, Avery P, Monkhouse L, King BP, et al. The impact of CYP2C9 and VKORC1 genetic polymorphism and patient characteristics upon warfarin dose requirements: proposal for a new dosing regimen. *Blood* 2005;106:2329-33.
- Rieder MJ, Reiner AP, Gage BF, Nickerson DA, Eby CS, McLeod HL, et al. Effect of VKORC1 haplotypes on transcriptional regulation and warfarin dose. *N Engl J Med* 2005;352:2285-93.
- Yuan HY, Chen JJ, Lee MT, Wung JC, Chen YF, Charng MJ, et al. A novel functional VKORC1 promoter polymorphism is associated with inter-individual and inter-ethnic differences in warfarin sensitivity. *Hum Mol Genet* 2005;14:1745-51.
- Viani GA, Afonso SL, Stefano EJ, De Fendi LI, Soares FV. Adjuvant trastuzumab in the treatment of her-2-positive early breast cancer: a meta-analysis of published randomized trials. *BMC Cancer* 2007;7:153.
- Netzer C, Biller-Andorno N. Pharmacogenetic testing, informed consent and the problem of secondary information. *Bioethics* 2004;18:344-60.
- Humphries SE, Hingorani A. Pharmacogenetics: progress, pitfalls and clinical potential for coronary heart disease. *Vascul Pharmacol* 2006;44:119-25.
- McLeod HL, Sargent DJ, Marsh S, Green EM, King CR, Fuchs CS, et al. Pharmacogenetic predictors of adverse events and response to chemotherapy in metastatic colorectal cancer: results from North American Gastrointestinal Intergroup Trial N9741. *J Clin Oncol* 2010;28:3227-33.
- Janssens AC, Gwinn M, Bradley LA, Oostra BA, van Duijn CM, Khoury MJ. A critical appraisal of the scientific basis of commercial genomic profiles used to assess health risks and personalize health interventions. *Am J Hum Genet* 2008;82:593-9.
- Garte S. Metabolic susceptibility genes as cancer risk factors: time for a reassessment? *Cancer Epidemiol Biomarkers Prev* 2001;10:1233-7.
- Caporaso N, Goldstein A. Cancer genes: single and susceptibility: exposing the difference. *Pharmacogenetics* 1995;5:59-63.
- Deenen MJ, Beijnen JH, Schellens JH. Is fluorouracil-induced severe toxicity in DPYD\*2A individuals related to sex or to treatment regimen? *J Clin Oncol* 2008;26:4997-8; author reply 8-9.
- Schwab M, Zanger UM, Marx C, Schaeffeler E, Klein K, Dippon J, et al. Role of genetic and nongenetic factors for fluorouracil treatment-related severe toxicity: a prospective clinical trial by the German 5-FU Toxicity Study Group. *J Clin Oncol* 2008;26:2131-8.
- McLeod HL, Krynetski EY, Relling MV, Evans WE. Genetic polymorphism of thiopurine methyltransferase and its clinical relevance for childhood acute lymphoblastic leukemia. *Leukemia* 2000;14:567-72.
- Krynetski E, Evans WE. Drug methylation in cancer therapy: lessons from the TPMT polymorphism. *Oncogene* 2003;22:7403-13.
- Nam RK, Zhang WW, Jewett MA, Trachtenberg J, Klotz LH, Emami M, et al. The use of genetic markers to determine risk for prostate cancer at prostate biopsy. *Clin Cancer Res* 2005;11:8391-7.
- Gerger A, Langsenlehner U, Renner W, Weitzer W, Eder T, Yazdani-Biuki B, et al. A multigenic approach to predict breast cancer risk. *Breast Cancer Res Treat* 2007;104:159-64.
- Ikediobi ON. Somatic pharmacogenomics in cancer. *Pharmacogenomics J* 2008;8:305-14.
- Oldenhuis CN, Oosting SF, Gietema JA, de Vries EG. Prognostic versus predictive value of biomarkers in oncology. *Eur J Cancer* 2008;44:946-53.
- Couzin-Frankel J. Cancer research. As questions grow, Duke halts trials, launches investigation. *Science* 2010;329:614-5.
- Potti A, Dressman HK, Bild A, Riedel RF, Chan G, Sayer R, et al. Genomic signatures to guide the use of chemotherapeutics. *Nat Med* 2006;12:1294-300.
- Baggerly KA, Coombes KR. Deriving chemosensitivity from cell lines: forensic bioinformatics and reproducible research in high-throughput biology. *The Annals of Applied Statistics* 2009;3:1309-34.
- Papadopoulos S, Kouvatseas G, Skarlos D, Malamos N, Delliou E, Saratsiotou I, et al. Comparison of HER2 detection methods between central and regional laboratories in Greece. *Clin Breast Cancer* 2007;7:784-90.
- Owens MA, Horten BC, Da Silva MM. HER2 amplification ratios by fluorescence in situ hybridization and correlation with immunohistochemistry in a cohort of 6556 breast cancer tissues. *Clin Breast Cancer* 2004;5:63-9.
- Perez EA, Roche PC, Jenkins RB, Reynolds CA, Halling KC, Ingle JN, et al. HER2 testing in patients with breast cancer: poor correlation between weak positivity by immunohistochemistry and gene amplification by fluorescence in situ hybridization. *Mayo Clin Proc* 2002;77:148-54.
- Whitehall V, Tran K, Umapathy A, Grieu F, Hewitt C, Evans TJ, et al. A multicenter blinded study to evaluate KRAS mutation testing methodologies in the clinical setting. *J Mol Diagn* 2009;11:543-52.
- Loh M, Liem N, Lim PL, Vaithilingam A, Cheng CL, Salto-Tellez M, et al. Impact of sample heterogeneity on methylation analysis. *Diagn Mol Pathol* 2010;19:243-7.
- Sequist LV, Joshi VA, Janne PA, Bell DW, Fidias P, Lindeman NI, et al. Epidermal growth factor receptor mutation testing in the care of lung cancer patients. *Clin Cancer Res* 2006;12(14 Pt 2):4403s-8s.
- Woelderink A, Ibarreta D, Hopkins MM, Rodriguez-Cerezo E. The current clinical practice of pharmacogenetic testing in Europe: TPMT and HER2 as case studies. *Pharmacogenomics J* 2006;6:3-7.
- Ibarreta D, Elles R, Cassiman JJ, Rodriguez-Cerezo E, Dequeker E. Towards quality assurance and harmonization of genetic testing services in the European Union. *Nat Biotechnol* 2004;22:1230-5.
- Printz C. BATTLE to personalize lung cancer treatment. Novel clinical trial design and tissue gathering procedures drive biomarker discovery. *Cancer* 2010;116:3307-8.
- LeBas J. The BATTLE Results Are In - Phase II trial reveals molecular signatures in lung cancer that may guide treatment decisions. *OncoLog* 2010;55.
- Altman DG, Bland JM. Diagnostic tests 2: Predictive values. *BMJ* 1994;309:102.
- Cross DS, Ivacic LC, Stefanski EL, McCarty CA. Population based allele frequencies of disease associated polymorphisms in the Personalized Medicine Research Project. *BMC Genet* 2010;11:51.
- Adeyemo A, Rotimi C. Genetic variants associated with complex human diseases show wide variation across multiple populations. *Public Health Genomics* 2010;13:72-9.
- Ferrusi IL, Marshall DA, Kulin NA, Leighl NB, Phillips KA. Looking back at 10 years of trastuzumab therapy: what is the role of HER2 testing?

- A systematic review of health economic analyses. *Per Med* 2009;6:193-215.
38. Elkin EB, Weinstein MC, Winer EP, Kuntz KM, Schnitt SJ, Weeks JC. HER-2 testing and trastuzumab therapy for metastatic breast cancer: a cost-effectiveness analysis. *J Clin Oncol* 2004;22:854-63.
  39. Veenstra DL, Higashi MK, Phillips KA. Assessing the cost-effectiveness of pharmacogenomics. *AAPS PharmSci* 2000;2:E29.
  40. McGuire AL, Diaz CM, Wang T, Hilsenbeck SG. Social networkers' attitudes toward direct-to-consumer personal genome testing. *Am J Bioeth* 2009;9:3-10.
  41. Davis JC, Furstenthal L, Desai AA, Norris T, Sutaria S, Fleming E, et al. The microeconomics of personalized medicine: today's challenge and tomorrow's promise. *Nat Rev Drug Discov* 2009;8:279-86.
  42. Hoop JG, Lapid MI, Paulson RM, Roberts LW. Clinical and ethical considerations in pharmacogenetic testing: views of physicians in "early adopting" departments of psychiatry. *J Clin Psychiatry* 2010;71:745-53.
  43. Marx-Stolting L. Pharmacogenetics and ethical considerations: why care? *Pharmacogenomics J* 2007;7:293-6.
  44. Corrigan OP. Pharmacogenetics, ethical issues: review of the Nuffield Council on Bioethics Report. *J Med Ethics* 2005;31:144-8.
  45. Lindpaintner K. Pharmacogenetics and the future of medical practice. *Br J Clin Pharmacol* 2002;54:221-30.
  46. Shah RR. Can pharmacogenetics help rescue drugs withdrawn from the market? *Pharmacogenomics* 2006;7:889-908.
  47. Proposed international guidelines on ethical issues in medical genetics and genetic services (part I). *Law Hum Genome Rev* 1998;8:219-23.
  48. Proposed International Guidelines on Ethical Issues in Medical Genetics and Genetic Services (Part II). World Health Organization, Human Genetics Programme. *Law Hum Genome Rev* 1998;9:239-51.
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