

# Concept and Putative Application of Pharmacogenetics and Pharmacogenomics

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## **Abstract**

Pharmacogenetics and pharmacogenomics, the study of how genotype affects drug response, represent a promising paradigm that aims to improve drug development, reduce adverse reactions, and maximize efficacy in drug dosage and prescription. This paper provides a foundation for understanding the scientific basis and putative application of pharmacogenomics for drug discovery, development, licensing and delivery to patients by discussing relevant terminology, types of genetic variation, and providing examples which highlight its multifaceted nature and complex mix of actors and interactions. From basic research to clinical trials, regulatory processes, marketing and prescription to patients, pharmacogenomics will interface with the regulatory and healthcare environment in a multitude of ways and will meet with resistance at various points. Its emergence will also demand the consideration of a number of ethical, legal and social implications, and may require the use of legislative and policy tools to ensure that the benefits of this technology are made available fairly and equitably.

## **Introduction**

The accumulation of genetic data, punctuated by the publication of the draft sequence of the human genome in February 2001, has provided the scientific community with information that should enable a better understanding of biological mechanisms and disease development in coming years and decades. To date, however, genetics-based treatments are few and far between despite widespread anticipation and media coverage, although there are claims that this is about to change.

One example of this is that mechanisms responsible for the wide variation in patient response to drugs, ranging from optimal efficacy to non-response to adverse reactions (ADRs<sup>1</sup>), are thus far largely unresolved. In the 1950s, Arno Motulsky first conceptualized and investigated the effect of inheritance on individual drug response, leading to a large and growing body of work now known as pharmacogenetics and only recently beginning to reach critical mass.<sup>2</sup> Through the linkage of specific gene, transcript or protein variants with specific response to medicines, pharmacogenetics (and its subsequent broadening, reflected in the term pharmacogenomics) aims to make drug discovery, development and delivery more rational. It is ultimately hoped that ADRs will be minimized and treatment efficacy increased, thereby improving health and health care in both human and monetary terms.

The safety and efficacy arguments for pharmacogenomics hold opportunities as well as challenges for various actors. For pharmaceutical companies, pharmacogenomics could increase the number of drug targets discovered, allow better discrimination between promising candidates and those with less potential, and improve the success rates of clinical trials. Regulators argue that elucidating robust correlations between genotype and drug response will speed up approval for effective candidates while reducing withdrawals that occur after a drug has entered the marketplace. Healthcare providers and insurers believe that pharmacogenomics will raise patient compliance and completion rates and reduce trial-and-error in prescribing. Health systems planners and decision-makers appreciate the potential monetary savings gained from avoiding ADRs, but must decide how to implement policies to harness the technology's benefits while minimizing its intrinsic threats and challenges.



Thus, the scientific foundation and putative application of pharmacogenomics remain difficult concepts to grasp. The complexity of the field necessitates clarity about what pharmacogenomics aims to do; complexity also means that its outcomes are likely to have multiple dimensions requiring consideration. This paper aims to serve as an introduction to pharmacogenetics and pharmacogenomics by exploring relevant terminology and the measurement of genetic variation, providing examples which highlight different aspects of the field, and discussing the role of genotype-phenotype correlation as applied to drug development. Far from being a clear-cut application of a scientific idea, pharmacogenomics is a multifaceted concept that is predicted to have effects at each of the discovery, development and delivery stages. In turn, the emergence and evolution of the discipline will raise a number of ethical, legal, social and policy issues that are now being investigated.

## Terminology and Concepts

### Pharmacogenetics and pharmacogenomics

It is first useful to define important terms given the technical nature of the topic. *Pharmacogenetics*, which became widely acknowledged in the 1990s, is based on the concept that inherited DNA, RNA, and protein-level differences influence metabolism and thereby individual patients' response to drugs. Those studying pharmacogenetics test the hypothesis *in vitro* and *in vivo* that the reason why certain patients respond well to a particular drug or dosage, while others do not, has a genetic basis.

*Pharmacogenomics* is a broader concept that examines the differential effects of various drugs across the genome or on the expression of multiple genes, largely *in vitro* (including DNA, RNA and proteins), and endeavours to develop new compounds to target these molecules.<sup>3</sup> Although conscious attempts to harmonize the various definitions of pharmacogenetics and pharmacogenomics have recently been made, including by the European Agency for the Evaluation of Medicinal Products<sup>4</sup>, in practice both terms are used loosely and interchangeably in the literature, as they are here.

The subtle distinction between pharmacogenetics and pharmacogenomics has relevance even though both link together genotype with drug response. Since pharmacogenetics is primarily concerned with patient reaction to a particular medicine (*i.e.* considers *patient* variability), it may be clinically useful to identify the most appropriate

medicine for an individual suffering from a particular disorder (given his/her genetic background) – “one drug across many genomes”. As part of the broader study of how patterns of gene expression respond to various drugs (*i.e.* *compound* variability), however, pharmacogenomics incorporates pharmacogenetic approaches but is also relevant to earlier stages of drug development, such as when considering which of a series of compounds to evaluate further – “many drugs across one genome”. As a result, while pharmacogenetics could be applied immediately to existing drugs and development programs, pharmacogenomics will exert its impact at the drug discovery stage and will thus appear in products over the longer term.

### Genetic variation: a diagnostic basis for pharmacogenomic testing

Despite the 99.9% genetic identity between two randomly chosen individuals, phenotype can still vary considerably in terms of physical features, disease susceptibility as well as drug response. While the statements of some industry leaders that up to 85% of the variance in patient reaction to drugs can be ascribed to genes may be controversial<sup>5</sup>, at least some of the variation in absorption, distribution, metabolism, and excretion of a medicine between individuals can clearly be attributed to the 0.1% genetic difference.

This genetic variation can take a number of forms, from changes in a single nucleotide to insertions or deletions of longer sequences. The most common (and lowest-level) sources of genetic differences are *single nucleotide polymorphisms* (SNPs), substitutions of one nucleotide for another at a given location. SNPs are deemed important enough that in 1999 the Wellcome Trust, partnering with ten major European and American pharmaceutical companies, provided initial funding for a SNP Consortium to create a high-density, publicly available SNP map of the entire human genome.<sup>6</sup> Finally, a combination of linked SNPs that travel together over time and space is known as a *haplotype*, and can also serve as a reliable marker to indicate potential drug response in patients. An international public-private consortium which includes Genome Canada and Genome Québec is aiming to develop a genomic ‘HapMap’ of these patterns for the public domain, using diverse DNA samples “with ancestry from parts of Africa, Asia and Europe”.<sup>7</sup> Given that many of these types of variation can exist at a given location in the genome, often in combination with other variants, research into the types of genetic variation recorded alongside drug response must be carefully considered and assessed.



Now that the number of SNPs that have been identified and characterized is growing, 'fingerprinting' technologies such as DNA, RNA and protein chips scan many sequences or molecules simultaneously and allow for rapid profiling to assess a person's risk for developing one or more diseases. The same tools could readily gauge the differential efficacy of a range of drugs for a given individual's genotype. Such chips could be designed in various ways, of which three stand out: one would be a chip to determine response to one company's range of drugs; a second would be a disease-specific chip to determine drug response across a range of medicines from different companies. A third option, which emerged in 2003 and is now being assessed by regulatory authorities, is a pharmacogenetic chip which tests for a number of variants in the cytochrome P450 family of enzymes, one of which, CYP2D6, metabolizes approximately 20-25% of medicines currently being prescribed.<sup>8</sup> Ultimately, industry experts, regulators and academics also envision a 'smart card' that would carry disease and drug information based on a range of molecular data. This could potentially save time and money by preventing ADRs and ensuring optimal drug prescription, but raises a number of technical and regulatory hurdles along with many ethical questions.

## Pharmacogenomics at Work

Three case studies will illustrate the complexity of the field, exhibit different aspects of its potential, and illuminate the opportunities and challenges it embodies.

### Pharmacogenetics by dosage – CYP2D6

Pharmacogenetic strategies involving CYP2D6 testing have not been utilized to a great extent in the clinic despite long-standing evidence of its role in drug metabolism (including codeine and clozapine, among others).<sup>9</sup> The over 70 known variants of CYP2D6 can result in a spectrum of activity, from poor metabolizers who experience adverse effects after accumulation of drugs in the body, to rapid metabolizers who only experience a therapeutic effect when prescribed drugs at a high concentration. However, adverse reactions associated with these variants are undesirable but rarely life-threatening, and alternative therapies are often available. The large number of alleles can also make the interpretation of molecular test results difficult and unreli-

able. In this case, then, a combination of mild ADRs, multiple treatment options, and low clinical validity and utility has kept pharmacogenetic testing for CYP2D6 out of mainstream clinical use. The CYP450 diagnostic chip may soon alter this equation by improving the speed, efficiency and interpretability of testing at this locus while lowering costs<sup>10</sup>.

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Because it is involved in the metabolism of so many medications, CYP2D6 encapsulates the dilemmas that pharmacogenetics and pharmacogenomics pose for both industry and regulators. The growing prevalence of genotyping during clinical trials provides useful data regarding efficacy and safety

for new drug candidates, but its disclosure during licensing applications may compel companies to restrict the availability of their medicines to narrowly targeted groups, thereby limiting market size and lowering the potential to recoup development costs. For regulators, there is a delicate balance between (a) accepting correlative data on genotype and drug response, which will help them to learn to better assess safety and efficacy, and (b) ensuring that the first experiences evaluating this data will not act as a disincentive for drug companies embarking on existing and future drug research and development programs. Partly to address these concerns, in November 2003 the U.S. Food and Drug Administration released draft guidelines for industry on the reporting of genotypic data gathered during drug trials.<sup>11</sup>

### Pharmacogenetics Under Study – Abacavir

GlaxoSmithKline (GSK) and Australian researchers have independently developed a pharmacogenetic test for Abacavir (ziagen), a licensed HIV/AIDS drug that causes serious and potentially fatal hypersensitivity reactions in approximately 5% of patients, usually within the first six weeks of therapy.<sup>12</sup> The researchers are attempting to identify genetic variants that lead to increased risk of ADRs, one of which, the HLA-B\*5701 allele, was found to be statistically significant in predicting hypersensitivity reactions to Abacavir in Caucasians.

It is important to note that some individuals lacking the HLA-B\* 5701 allele are hypersensitive to Abacavir, while some with the flagged variants are tolerant; the former inconsistency was particularly evident in patients of African



descent. Since the test clearly cannot be considered an absolute predictor of drug response, it is thus difficult to apply the findings to other populations. Perhaps for this reason, the official GSK labelling of Abacavir acknowledges ADRs but does not identify genetic risk factors.<sup>13</sup> Equally intriguing, while the Australian researchers have incorporated this testing into clinical practice, GSK does not advise testing for patients who have experienced hypersensitivity reactions, ostensibly in order to identify a combination of variants with greater sensitivity and specificity.

### **Pharmacogenomics in the market: Herceptin**

Herceptin (trastuzumab) is a breast cancer treatment that is particularly effective in a subgroup of patients whose tumours express abnormally high amounts of the HER2/neu protein.<sup>14</sup> Up to 30% of breast cancer patients fall into this category, and have a higher incidence of metastasis, drug resistance, and a shorter survival time than patients lacking HER2/neu over-expression.<sup>15</sup> Women with this phenotype who are prescribed Herceptin stay cancer-free 65% longer than those patients on standard chemotherapy, although there are reports of adverse events including cardiac dysfunction, anaphylaxis, and an increased risk of infection.

Testing of tumour tissue from women with breast cancer can identify patients who over-express HER2/neu and are likely to benefit from Herceptin. This procedure was adopted at an early clinical trial stage by screening patients and pre-emptively eliminating non-responders, allegedly resulting in one-ninth the Stage III trial size that would have otherwise been required.<sup>16</sup>

The Herceptin case illustrates a number of tensions facing health care insurers, particularly for the UK's publicly-funded National Health Service (NHS). Although the medicine was licensed in 2000 and paid for by some hospitals and health authorities, the NHS postponed a decision on nation-wide funding until its National Institute for Clinical Excellence (NICE) could evaluate the medicine's cost compared with clinical efficacy and gains in life expectancy and quality of life. In the interim period before NICE's appraisal, some women had to pay for Herceptin privately while others were provided it by the NHS, leading to allegations of inequitable provision (and a "post-code lottery") depending on where one resided.<sup>17</sup> Ultimately, NICE's recommendation was to provide Herceptin in England and Wales for certain women with HER2-positive breast cancer, and therapy is now being provided to all eligible patients across the NHS.<sup>18</sup>

### **Comparing and Contrasting**

Further examples of pharmacogenetics include the prescription of 6-mercaptopurine for childhood leukaemia depending on functionality of the *TPMT* gene, and polymorphisms in neurotransmitter receptor and transporter genes that affect response to certain antipsychotic medications.<sup>19</sup> However, *CYP2D6*, Herceptin and Abacavir form an interesting study for a number of reasons: all are associated with molecular diagnostic tests, and have recently demonstrated new challenges for developers and regulators. Their contrasts are also noteworthy. First, Herceptin treats cancer, while Abacavir aims to treat an infectious disease and *CYP2D6* metabolizes a range of drugs for a variety of diseases. Second, at the molecular level, Herceptin is prescribed on the basis of acquired tumour protein expression, whereas Abacavir- and *CYP2D6*-related testing assesses variance in the inherited (constitutional) genome itself. Finally, Herceptin emphasizes efficacy in patients with a particular tumour expression profile; conversely, Abacavir will presumably be prescribed to patients in a manner that avoids hypersensitivity reactions, *i.e.* with safety foremost in mind, while *CYP2D6* information allows for *both* safety and efficacy through dosage adjustment. The fact that pharmacogenetics and pharmacogenomics can be so multifaceted has an array of implications for drug discovery, development, and regulatory approval.

### **The Putative Application of Pharmacogenomics**

From these examples, it is clear that the complex nature of drug discovery/design, development and delivery will interface with the regulatory and healthcare environment in many ways. As discussed in this section, pharmacogenomics will impact and be impacted by these environments and will meet with varying degrees of resistance.

#### **Drug Discovery and Development: Improving the Scope for Target Selection**

Drug research and development is a time, resource, and financially intensive process. On average, a successful drug takes 10-15 years, hundreds of researchers, and thousands of trial subjects to progress from earliest research through to market. Approximately one out of every 5,000 compounds initially evaluated is eventually approved, and up to 75% of discovery and development costs are attributed to failed products.<sup>20</sup> In total, it may cost US\$880 million or more to produce one successful medicine<sup>21</sup>, although some have





expressed scepticism over these figures.<sup>22</sup> As a result, the discarding of unsuitable compounds is an ongoing and important occurrence.

In recent years the pharmaceutical industry has been concerned with a decline in products submitted to regulatory agencies for approval, combined with the upcoming expiration of many high-revenue drug patents.<sup>23</sup> R&D costs, meanwhile, continue to escalate. Through a better understanding of underlying molecular pathways of disease, it is hoped that pharmacogenomics will move the development process away from trial-and-error drug discovery and towards rational drug design. This would result in more viable drug candidates, improved industry success rates, and more efficacious interventions, which there is great potential for given that only 450 of an estimated 10,000 legitimate drug targets in the human genome are currently known.<sup>24</sup> However, new candidates and targets will require novel (and costly) validation and characterization chemistries, and are more likely to have adverse effects that are only picked up at the trial level, after substantial discovery costs have accumulated. Thus, while enthusiastic about the potential of pharmacogenomics, industry representatives are concerned about how it will financially impact their companies.

### ***Smaller, Shorter, Cheaper Clinical Trials***

Pharmacogenomics could allow trial populations to be selected based on genetic data, which may have two consequences. First, initial diagnostic tests could link polymorphisms or expression patterns with ADRs at an early stage in clinical trials, allowing companies to abandon suspect compounds at a less costly point. Although this might signal a shift away from the current likelihood that companies or regulators would halt development even when ADRs occur in only a small percentage of a trial population, the utility of pharmacogenomic strategies for eliminating ADRs has been assessed and questioned.<sup>25</sup> Second, genotype-phenotype correlation studies could maximize efficacy by identifying patients for whom a drug will be of ideal benefit. This would reduce end-stage trial sizes (and overall drug development costs) by selecting individuals with optimal response genotypes. A smaller and more homogenous

subject group would lead to clinical results that are clearer and more indicative of the factor being evaluated, making drugs more likely to progress through the regulatory process.

One limitation to this would be the comparatively small numbers of subjects enrolled (and shorter time-scales involved) in early-stage trials; this could be moderated to

some degree by focusing on genes and proteins thought likely to be involved in the metabolism of a particular medicine (rather than randomly selected markers), with the acknowledgement that more subtle effects would probably be missed.<sup>26</sup> To the extent that this is not possible, either larger Phase I trials will be required or, less ideally, later stages could

be used as a testing ground for further genotype-phenotype correlation studies. Additionally, since pharmacogenomics holds the promise of smaller late-stage trials but has yet to be put into practice on a large scale, formal and costly regulatory monitoring of post-licensing (Phase IV) outcomes is likely to intensify.

## ***Regulatory Approval, Marketing and Drug Delivery***

In addition to the recent FDA guidance clarifying data submission during licensing applications, pharmacogenomics should encourage regulatory coordination at both intra-national and international levels. Within national agencies, pharmacogenomics has influenced integration between offices that assess the licensing and prescription of new clinical entities with those that regulate and approve linked tests and other medical devices.<sup>27</sup> Internationally, since the prevalence of certain drug response-related gene variants will differ across regions and populations, regulatory agencies will also need to effectively record and share information collected in one jurisdiction with others to ensure that safety remains paramount. To that end, the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use has recommended that additional studies be conducted when drugs are submitted for licensing in new jurisdictions.<sup>28</sup>

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It has also been argued that pharmacogenomics could allow medicines that previously failed regulatory hurdles (because of safety or efficacy concerns) to be re-assessed.<sup>29</sup> With genetic or genomic profiling prior to prescription, there is now a possibility of administering these so-called ‘lost’ drugs to only a well-defined safe population (avoiding individuals likely to respond adversely), permitting prescription for those who will respond optimally and allowing at least some research and development expenditures to be recouped. However, the actual feasibility of this has been questioned for both marketing and logistical reasons.<sup>30</sup>

Health economics studies, and particularly cost-effectiveness criteria, are increasingly important when considering new treatments and therapies in the face of a limited budget, and health care payers are creating institutions (such as NICE) to recommend which drugs, therapies and interventions can be funded in the context of scarce resources. Advocates of pharmacogenomics claim that greater effectiveness could result from more efficacious treatments with better quality of life; lower costs could result from smaller trials, fewer errors in prescribing, and the ensuing higher completion rates and decreased adverse reactions.

Because of greater safety and efficacy, higher completion rates (less reliance on trial-and-error prescribing) and increased patient compliance, physicians may be more likely to prescribe pharmacogenomics-based drugs, although further education for health professionals may be required. This underscores the need for evaluating training regimes and the way in which responsibilities have been divided amongst the various health professions. If this is handled well, the safety and efficacy benefits of pharmacogenomics could eventually offset the additional cost of genetic testing to determine the optimal drug for a particular patient. One can even imagine a time when insurers would require testing in order for patients to submit reimbursement claims.

### **Selected Ethical, Legal and Social Issues**

A number of ethical, legal and social issues arise throughout the R&D, licensing, and delivery stages of medicines based on pharmacogenomics. The use of pharmacogenetic information collected in research has been discussed in the litera-

ture, including issues of consent, privacy and confidentiality, and individual feedback provided by researchers to participants.<sup>31</sup> However, questions of equity of access versus ability to pay, legislative and policy tools that might encourage drug development, and the extent to which pharmacogenomic information resembles information on genetic susceptibility to disease have also remained contentious.

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A paradox of pharmacogenomics is that it aims to produce safer and more effective drugs by stratifying existing patient populations. This stratification could result in a range of more efficacious treatments, but each with decreased revenue due to

market segmentation, leading to speculation that the application of these technologies may cause an even greater dearth of drugs for some small, ‘non-profitable’ patient populations.<sup>32</sup> In the interest of equity, can and should governments provide incentives for manufacturers to develop medications for under-served populations (defined by molecular profile, distinct symptoms or morphology – or even, directly or indirectly, ability to pay)? Would doing so inadvertently feed into public beliefs that individuals are defined and bound by their genetic makeup? This is of particular concern if genotype-phenotype associations are shown to coincide with socially defined notions of race, as has been debated.<sup>33</sup> In that case, and given the correlation between race and ethnicity with socio-economic status, in the absence of such incentives it is possible that future development (or lack thereof) of a drug candidate will hinge on its utility for profitable populations or sub-populations.

One solution that has been advocated is for the use and potential expansion of orphan drug laws, which provide tax breaks and financial incentives for research and development in the area of rare (and thus unprofitable) disorders, to be created or fine-tuned bearing pharmacogenomics in mind. In the USA, the 1983 *Orphan Drug Act* has been credited with invigorating R&D into interventions for neglected diseases, and other jurisdictions such as Australia, the European Union and Japan have passed similar legislation (although Canada has not).<sup>34</sup> The degree to which these policies will provide sufficient incentive for companies to develop drugs for small, pharmacogenomics-based disease sub-populations en masse, remains to be seen.



At the level of treatment and clinical practice, it has been claimed that pharmacogenetic testing is less ethically problematic than testing regarding genetic susceptibility to disease, since the former reveals information on what to prescribe rather than future risk of illness. However, the robustness of this distinction is unclear, as three examples will demonstrate. First, pharmacogenetic information could reveal that there is *no* optimal drug for a patient's genotype; second, it could reveal a particular disease sub-category which is associated with a "distinct prognosis" or acuteness of condition, such as with HER2/neu overexpression; third, it could unveil information about susceptibility to diseases or response to other drugs, as in the case of CYP2D6 (which metabolizes multiple medicines). In each of these instances, the implications of pharmacogenetic testing overlap with those of genetic testing for disease susceptibility, suggesting that the boundaries between the two are not as impermeable as might be initially thought. While the middle case is particularly relevant for cancers which involve diseased tissue, the latter holds for variation in the inherited (constitutional) genome. Thus, questions of clinical judgement, patient choice, and consent in pharmacogenetics, along with other ethical, legal and social issues, will remain complex and perplexing.

## **Conclusion – Pharmacogenetics and Pharmacogenomics in Perspective**

From this introductory analysis, it is clear that pharmacogenetics and pharmacogenomics will impact upon the research, regulatory, and healthcare environments and many types of health organizations. While a number of pharmacogenetic tests, drug candidates and licensed products are currently being studied, developed and marketed, their examples raise a multitude of scientific, clinical, regulatory, policy, legal and ethical issues pertaining to drug discovery and design, development through clinical trials, licensing and delivery to patients. Ironically, pharmacogenomics – which to many represents the segmentation of patient populations into smaller and smaller groups – will require various actors to work more closely together than ever in an attempt to better understand and coordinate drug development, regulatory issues and health policy.

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