Priority Medicines for Europe and the World
"A Public Health Approach to Innovation"

Update on 2004 Background Paper

Background Paper 7.4
Pharmacogenetics and Stratified Medicine

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Glossary of Terms

Adverse drug reaction: an unintended, harmful reaction to medicines.

Biobank: collection of biological samples and associated information stored for research purposes.

DNA: molecule that carries the genetic information in a cell. DNA composed of nucleotides.

DNA methylation: biochemical process in which a methyl group is added to cytosine or adenine nucleotides.

Disease profiling: genetic or molecular profiling of disease.

Enzyme: protein involved in a specific chemical conversion.

Exome: part of the genome formed by DNA sequences that encode genes (exons).

Gene: segment of DNA coding for an inheritable characteristic.

Genetic variation: naturally occurring genetic differences between individuals.

Genome: total content of genetic information in a cell.

Genotype: genetic constitution of an individual.

Genome-Wide Association Study (GWAS): study to assess common genetic variations across the entire genome of a large population of individuals in order to study whether any of the investigated variations is associated with a phenotype of interest.

Linkage studies: Genetic linkage is the tendency of DNA segments to be inherited together. A genetic linkage studies aims to identify a genetic marker that inherits with the (unidentified) gene associated with the phenotype of interest.

Metabonomics (or metabolomics): study of the effect of a systematic change in a biological system caused by an intervention (such as drug administration or specialized nutrition).

Monogenetic trait: phenotype caused by one single gene.

Non-coding RNA: RNA molecule that is not translated into a protein.

Pharmacoeigenomics: assessing the relationship between variation in physical DNA structure and treatment outcome.

Pharmacogenetics: assessing the relationship between variation in a gene and treatment outcome.

Pharmacogenomics: assessing the relationship of variation in various genes (or genome-wide) and treatment outcome.

Phenotype: observable characteristics of an individual, e.g. disease or poor treatment response.

Polygenetic trait: phenotype caused by multiple genes.

Proteomics: study of the proteome; the regulation and production of the proteins in a cell.

Quality adjusted life year (QALY): measure of the quality of remaining life-years. Often used in cost-effectiveness analysis.

SNP: Single Nucleotide Polymorphism is the most common type of genetic variation, in which a single nucleotide is altered at a certain position in the genome.

Transcriptomics: study of the transcriptome; the RNA transcripts produced by the genome and the regulation of that process.
**Executive Summary**

Stratified or personalised medicine is a rapidly developing field that will have major impact on healthcare in the coming decades. Without applying the concept of stratified medicine, a particular treatment is targeted to the whole patient group, without being able to predict the treatment response in patients. Stratified medicine allows medicines to be targeted to those patients who (best) respond to therapy and/or to be avoided in patients who are most likely to experience side effects. Thus, stratified medicine shows great promise in the improved and safer usage of existing medicines in high, as well as low, resource settings. In addition, it demonstrates potential for the identification of new drug targets and the development of new diagnostic tools. The term ‘stratified medicine’, however, might be more accurate than the term ‘personalised medicine’ in encompassing the potential and hopes of the new -omics era for medicine and public health, in which the main focus will be in the stratification of patient populations on the basis of biomarkers (e.g. genetic variations and protein expression). Scientific technologies in the field of genomics and biomarker discovery are advancing at a rapid pace, shifting from single to complex multifactorial diseases and from monogenic (assessing one single gene) to polygenic (assessing multiple genes at the same time) approaches. Despite the rapid scientific advances, the implementation of stratified medicine in health care systems remains low. This is due in part to (current) scientific limitations, and the lack of standardization for response outcomes (i.e. adverse drug reactions which complicate the comparability of studies), which complicates the comparability of studies. Furthermore, successful replication is generally low, and a global or European pharmacogenomic database with a thorough inventory of available knowledge and biological specimens is lacking. Moreover, societal and regulatory limitations hinder implementation; there is a need for a well-organised technology infrastructure, professional training in the use and interpretation of testing, as well as internationally aligned ethical, legal and regulatory frameworks. A summary of research and policy priorities for stratified medicine is given in Box 7.4.1. The clinical implementation of stratified medicine also requires basic, translational, as well as regulatory studies.

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**Box 7.4.1: Key Summary of Research and Policy Priorities for Stratified Medicine**

- Establishing a funded European research network
- Safer use of existing medicines is underused
- The effect of non-genomic factors influencing treatment response should not be underestimated
- Need for a European catalogue of pharmacogenomic datasets and harmonization program
- Current regulatory guidelines and reimbursement procedures hamper implementation
- Stratified medicine in low resource settings is rare
- Stratified medicine in vulnerable groups should be stimulated
- Clinical added value should be assessed
- Barriers to implementation should be diminished
- Ethical, legal and social implications of stratified medicine should be further investigated
1. Introduction

Stratified medicine is a rapidly developing field that is likely to have important clinical consequences in the coming decades. It holds strong promise for the improvement of both the drug efficiency and the drug safety of existing drugs due to the identification of drug responders and non-responders based on biological markers (see Box 7.4.2: the abacavir case). Furthermore, as a result of increasing knowledge about complex multifactorial diseases, the identification of new drug targets and the development of new diagnostic tools will also be possible.

Genomics and other –omic technologies are rapidly evolving and are key elements in the future of stratified medicine. Historically, human diseases have been treated on a ‘one-size-fits-all’ basis where one drug suits all patients. The choice of a drug has been guided by evidence-based information, professional guidelines and a ‘trial-and-error’ approach. When a patient does not respond adequately with a prescribed drug or showed substantial adverse drug reactions, the dosage can be adjusted or the medicine itself might be replaced by another. However, with the unravelling of the molecular pathways underlying disease processes and the rapid emergence of new -omic technologies (including epigenomics, proteomics and metabonomics), research is rapidly producing new insights that will open the door to more tailored forms of drug selection, drug dosing, drug development and diagnostics. In this chapter we will focus mainly on the role of pharmacogenomics in stratified medicine, as this particular field has been most successfully translated into clinical practice in comparison to the other -omics fields. Pharmacogenomics study the influence of genomic variation on treatment response. Two successful pharmacogenomics examples include HLA-B*5701 genotyping and the risk of hypersensitivity to the antiretroviral treatment abacavir and HER2 testing in breast tumour biopsies and clinical response to the antineoplastic agent trastuzumab.

Based on individual or disease-specific biomarkers, the drug choice can be tailored in order to improve efficacy and to minimize the occurrence of adverse drug reactions. In addition to tailored treatment, -omics advances also hold promise for new approaches to drug development and a better use of existing drugs, as well as the prevention of disease by the identification of individuals at risk. Nevertheless, despite the predictions that the era of stratified medicine has arrived, clinical implementation has been limited.1 In this paper we will address the evolution of the field, its current level of development, as well as the challenges and opportunities for future research and for implementation in clinical practice.
Box 7.4.2: The abacavir case; uptake of genetic HLA-B*5701 testing

In 1998, abacavir, an anti-retroviral treatment for HIV was approved by the FDA and in 1999 by the EMEA (now EMA). The drug was generally well tolerated; however, it caused a drug hypersensitivity reaction in a small group of patients (5 to 8%) that could be life-threatening. From 2001 onwards there was increasing evidence of a relationship between a genetic variation in the HLA-B*5701 gene (a gene that codes for a protein involved in immunity) and the risk of abacavir hypersensitivity. Sales of abacavir containing drugs subsequently declined. A genetic test to assess the HLA-B*5701 was introduced in 2005, but test utilization remained low due to concerns about differences in HLA-B*5701 prevalence between individuals of different populations and residual risks upon negative genetic results (See Figure 7.4.1 for test uptake in the United States). A shift took place in 2007 upon the completion of two industry-sponsored studies that showed the generalizability of the genetic test across diverse geographical patient populations and patients with different genetic ancestry and a very high negative predictive value. This together with the development of a skin patch test to immunologically confirm the genetic test led to the rapid adoption of HLA-B*5701 testing by HIV practitioners and the incorporation of the test in clinical guidelines. It was only in July 2008 that the FDA included HLA-B*5701 testing recommendations on the drug label of abacavir. Genetic testing of HLA-B*5701 kept abacavir on the market because it is now possible to target the drug to a patient population with almost no risk in developing the severe hypersensitivity reaction.

Figure 7.4.1: uptake of genetic testing of HLA-B*5701 in the US

![Graph showing uptake of genetic testing of HLA-B*5701 in the US](image)

2. From personalised medicine to stratified medicine

The term ‘personalised medicine’ is increasingly being replaced by the term ‘stratified medicine’.4 According to the European Commission workshop report ‘Stratification biomarkers in personalised medicine’ from 2010, personalised medicine may be defined as ‘a medical model using molecular profiling technologies for tailoring the right therapeutic strategy for the right person at the right time, and determine the predisposition to disease at the population level and to deliver timely and stratified prevention’.5 Genomic and non-genomic biomarkers will enable us to increasingly target treatment specifically to subpopulations of patients who are more likely to respond to a particular treatment and are less likely to develop adverse drug reactions, and will lead to ‘subpopulation-unique’ instead of to ‘individual-unique’ drug targeting and development (Figure 7.4.2). In this way, the benefit-risk profile of the medicine can be assessed per population stratum, and unnecessary (in case of non-response) or harmful (in case of toxic effects) use of medicines may be prevented. In this sense the other cross-cutting themes in this background paper (children, women and the elderly) are also examples of stratified medicine.

A recent report of the United States National Academy of Sciences on the development of a new framework for the taxonomy of human disease, however, advocates the term ‘precision medicine’ for ‘the use of genomic, epigenomic, exposure, and other data to define individual patterns of disease, potentially leading to better individual treatment’.6 While the term ‘stratified medicine’ reflects the realistic effect on patient/population-level, ‘precision medicine’ reflects the clinical consequences — a better treatment. Both terms seem to reflect more precisely the promises and hopes of the new genomic era than ‘personalised medicine’, which might have been an overambitious definition promising individualised unique drug targeting and development. In this report we will use the term ‘stratified medicine’.

Figure 7.4.2: Concept of stratified medicine. Biomarkers will enable us to target treatment specifically to subpopulations of patients who are more likely to benefit from a particular treatment.

Source: http://www.pharmainfo.net/reviews/role-pharmacogenomics-drug-development.
3. From monogenic to polygenic approaches

In April 2003, the human genome project was declared complete with the sequencing of 99% of the human genome. From 2003 onwards, data production in the field of genomics has continued to grow exponentially, and instead of focusing on the human genome as an end in itself, genomic researchers have turned their attention towards the role of DNA, RNA, proteins, and metabolites in disease aetiology. As part of this trend toward more complexity, interest shifted from the relatively rare monogenic diseases, which result from modifications in a single gene, such as Huntington’s disease, cystic fibrosis and thalassaemia, to the more common complex diseases, including cardiovascular disorders, type 2 diabetes, cancer, depression, and Alzheimer disease.

Simultaneously with the genomic revolution, the evolution of pharmacogenetics into pharmacogenomics took place. Pharmacogenetics is the study of variations in a single gene as related to drug response, whereas pharmacogenomics is often described as the whole-genome application of pharmacogenetics where variations in multiple genes are assessed at the same time. Although both terms are still used interchangeably, the term ‘pharmacogenomics’ is broader and also includes new genome-wide DNA technologies and RNA.

Successful early examples of pharmacogenetics involve identifying variations in genes coding for drug metabolism enzymes which influence drug concentration and have major effects on therapy response or the occurrence of side effects: thiopurine methyltransferase (TPMT) and CYP2D6, for example. The enzyme thiopurine methyltransferase is involved in the methylation of thiopurine drugs. Thiopurines are widely used to treat acute lymphoblastic childhood leukaemia (ALL), inflammatory bowel disease, autoimmune diseases and organ transplant recipients. Genetic variation in the gene coding for this enzyme influences the enzyme activity. Approximately 10% of individuals have lower activity for this enzyme (carriers of one gene variant: heterozygotes) and 0.3% lack enzyme activity (carriers of two gene variants: homozygotes), and are very susceptible to severe haematological toxicity when treated with thiopurine drugs (i.e. azathioprine and 6-mercaptopurine) due to a slower metabolizing of the drugs. In 2004, the U.S. Food and Drug Administration (FDA) recommended TMPT testing prior to the start of treatment with azathioprine with a message on the product label of the drug, in order to enable the adjustment of individual treatment dosages.

Cytochrome P450 2D6 (CYP2D6) codes for debrisoquine-sparteine hydroxylase, an enzyme involved in the metabolism of xenobiotics, and is implicated in the oxidation of 20-25% of all clinical drugs (including various antidepressants, antipsychotics and antiarrhythmic). Variations in the gene can lead to altered enzyme activity, based on the presence of these variations individuals can be classified as: ‘poor’, ‘intermediate’, ‘extensive’ and ‘ultrarapid metabolizers’. Approximately 7% of Caucasians are poor metabolizers, due to two variant CYP2D6 alleles. These individuals may suffer from adverse drug reactions when treated with standard xenobiotic drug dosages, or may not respond to drugs that require activation by the enzyme. Conversely, ultrarapid metabolizers (estimated to be ~1% of the Caucasian population) may also suffer from adverse drug reaction due to the toxicity of prodrugs that need to be activated by the enzyme, or a lack of therapeutic effect when treated with standard drugs with a narrow therapeutic window. In 2004, a microarray based
pharmacogenetic test, the Roch AmpliChip 450 test was approved for clinical use in the EU, and in 2005 in the United States.\textsuperscript{15, 16} It has been used mostly in psychiatry, but is thought to be valuable in the oncology field as well.\textsuperscript{13}

CYP2D6 and TMPT both act according to a monogenic model where variation in one single gene has a substantial influence on drug concentration and thereby drug effect. However, with the rapid advances in genomics, it became increasingly clear that multiple proteins participate in the metabolism of most drugs. Therefore, in order to evaluate the full contribution of genetic variation in drug response, multiple genes in a drug signalling pathway should be studied concurrently.\textsuperscript{10} This approach requires large numbers of cases in order to have enough statistical power to identify the small effects of common gene variants.

### 4. Biomarkers and disease profiling

The summary report of the workshop ‘Stratification biomarkers in personalised medicine’ organized by the Directorate General for Research and Innovation of the European Commission\textsuperscript{5} defined biomarkers as follows: ‘A biological characteristic, which can be molecular, anatomic, physiologic or biochemical. They act as indicators of a normal or a pathogenic biological process. They allow assessing the pharmacological response to a therapeutic intervention. A biomarker shows a specific physical trait or a measurable biologically produced change in the body that is linked to a disease or a particular health condition’. The report describes four distinct types of biomarkers based on the purpose for which they are used: 1) diagnosis (in patients), 2) risk assessment (in healthy individuals), 3) prognosis of disease (in patients) and 4) treatment prediction (in patients) (Table 7.4.1).

Scientific literature shows an explosion in the discovery of biomarkers, however, only a few have been validated for routine clinical practice.\textsuperscript{17} So far, most advances have been made in the oncology field, in which molecular and genetic tumour profiling is increasingly used to predict therapy response and/or prognosis. An important factor in the success of tumour profiling is the development of targeted therapies in which drugs block the tumour by binding to tumour-specific molecules. A classic case of a targeted therapy and associated biomarkers is trastuzumab (trade-name: Herceptin\textsuperscript{®}) and HER2 testing. Trastuzumab is a chemotherapy agent that can block human epidermal growth factor receptor 2 (HER2). This protein is encoded by the ERBB2 gene and the gene is overexpressed in approximately 15-30% of the patients with breast cancer.\textsuperscript{18} Only patients with high levels of HER2 are likely to respond to trastuzumab.\textsuperscript{19} In 2006, the FDA and European Medicines Agency (EMA) approved trastuzumab for the treatment of HER2 overexpressing breast cancer and in 2010 for HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma,\textsuperscript{20, 21} and HER2 testing has been imbedded in clinical guidelines.\textsuperscript{22} Another successful example of a targeted anti-cancer therapy is imatinib (trade-name: Gleevec\textsuperscript{®} (USA) or Glivec\textsuperscript{®} (EU)). The treatment blocks the working of a tumour-specific enzyme, which is often produced in chronic myelogenous leukaemia and gastrointestinal stromal tumours. Blockage of this enzyme inhibits tumour development and the activity of the enzyme is frequently monitored in patients using imatinib in order to monitor the efficiency of the treatment.\textsuperscript{23}
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Tumour profiling can also be used for prognostic purposes such as in the case of MammaPrint® (or 70-gene strategy). The test assesses the expression of 70 genes from breast cancer biopsies in order to predict the risk of reoccurrence of the breast cancer and to guide treatment with adjuvant chemotherapy.²⁴ It classifies patients into ‘low’ or ‘high’ risk for the reoccurrence of breast cancer. MammaPrint® became available in Europe in 2004, and the FDA cleared the MammaPrint® as a diagnostic tool for the United States market in 2007.²⁵ A large prospective multi-centre trial (MINDACT) with 6 000 breast cancer patients is being performed to validate the guidance of treatment based on the combination of the MammaPrint® and the establishment of standard clinical criteria is currently ongoing.²⁶ Cost-effectiveness models suggest a high likelihood of cost-effectiveness for the MammaPrint® compared to standard clinical guidelines.²⁷, ²⁸ In a cost-effectiveness analysis based on three MammaPrint® validation studies where MammaPrint® was compared to the clinically used guidelines of St. Gallen and Adjuvant Online software, it was shown that MammaPrint® had lower total health care costs per patients compared to St. Gallen (€28 045, respectively, €35 475), but higher total costs than Adjuvant Online Software (€26 915). Nevertheless, MammaPrint® yielded more quality adjusted life years (QALY) (12.44) compared to Adjuvant Online Software (12.20) or St. Gallen (11.24) ²⁷. It should be noted that the gain is limited and leads to the question of how much society is willing to pay for gained QALY’s. Compared to the Adjuvant Online strategy the 70-gene strategy was estimated to costs €4 614 per QALY gained.

### Table 7.4.1: Classifying biomarkers according to test outcome

<table>
<thead>
<tr>
<th>Type of biomarker</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnostic</td>
<td>Genetic testing of the Huntington’s disease gene in an individual with suggestive symptoms in order to confirm diagnosis.</td>
</tr>
<tr>
<td>Susceptibility/risk</td>
<td>Genetic testing of the Huntington’s disease gene in an individual with a family history of the disease but without symptoms in order to assess the risk of Huntington’s disease later in life.</td>
</tr>
<tr>
<td>Prognostic</td>
<td>Assessment of the expression of a set of genes with the MammaPrint® in a tumour biopsy of a breast cancer patient to assess the risk of reoccurrence of the disease and the need for additional chemotherapy.</td>
</tr>
<tr>
<td>Predictive (for treatment response)</td>
<td>Measurement of HER2 protein levels in the tumour biopsy of a breast cancer patient to predict response to trastuzumab treatment</td>
</tr>
</tbody>
</table>


Disease profiling and targeted therapies are not restricted to the oncology field. Disease profiling and guiding of treatment also occur in other fields, including the treatment of infectious diseases such as HIV²⁹ and inflammatory diseases such as asthma, where promising results are being seen for anti-interleukin-13 treatment lebrikuzimab. The drug was successful in Phase 2 studies with asthmatic patients unresponsive to standard...
glucocorticoid therapy, especially in patients with a disease characterized with high levels of the serum protein periostin. Periostin is thought to be a surrogate biomarker for the level of interleukin-13.\(^{30}\)

In the case of lebrikizumab, periostin can be measured in the blood serum of individuals; nevertheless, a general limitation of disease profiling is the need of local ‘disease’ tissue, which often requires an invasive procedure to measure locally produced proteins or molecules. Pharmacogenomics, however, focuses on the genetic variations that influence therapy response; these genetic variations are present in all tissue and can generally be measured in DNA obtained non-invasively through mouth swabs or saliva.

5. Research

5.1 Study design

Generally, there are three types of epidemiological study design for pharmacogenomic studies:\(^{31}\) 1) randomized clinical trials (RCT), 2) observational case-control studies and, 3) studies based on biobanks (potentially linked to electronic health records) (Figure 7.4.3).

Currently, Randomized Clinical Trials (RCT’s) are the gold standard in drug research (See Background Paper 8.4). In a RCT, an individual is randomized to a specific treatment/placebo or alternative medication, often using a double-blind method: neither the study participant nor the researcher knows to which treatment the individual is assigned. Due to the randomization and regular monitoring, bias and confounding are minimal. The European Pharmacogenetics of AntiCoagulant Therapy-study (EU-PACT) is an example of a pharmacogenomics RCT. This study, financed by the Seventh Framework Program (FP7) of the EU, focuses on genetic variation and oral coagulation drugs (coumarin derivatives) in the prevention of thrombotic disorders. These drugs have a narrow therapeutic window; the dosage needs to be high enough to prevent blood clotting, yet not high enough to cause severe bleeding. The correct dosage differs from person to person. Various factors, including age, sex, diet and co-medication, as well as genetic variation (especially in the CYP2C9 and VKOR genes) are thought to play a role. The EU-PACT study is an ongoing multi-centre trial in 7 European countries and compares two coumarin dosages strategies: 1) dosing based on clinical information and genotype, and 2) dosing based on clinical information alone (standard care).\(^{32}\) In addition to the added clinical value, EU-PACT will also assess the cost-effectiveness of this pharmacogenomics approach.

Another example is the recently published RCT based on prospective testing of genetic variation in the ADRB2 gene in 62 children with chronic asthma. Asthmatic children homozygous for the variant genotype seemed to benefit more from a leukotriene antagonist than from a long-acting beta(2)-agonist. Children (homozygous for the variant genotype) were randomized to a long-acting beta(2)-agonist combined with an inhaled corticosteroid (LABA and ICS) or to a leukotriene antagonist combined with an inhaled corticosteroid (LTRA and ICS). The ICS and LTRA group scored better on asthma symptoms and quality of life, used less rescue medication and were absent fewer days from school when compared to
the group of children treated with LABA and ICS. These results are particularly interesting since they demonstrate a genetic effect on the efficacy of existing medicines.

Figure 7.4.3: A visual display of the three primary epidemiologic study designs used in pharmacogenomics: randomized clinical trials, case–control and biobanks.

A RCT can only be performed when relevant genetic variations have already been identified, and they are time consuming and costly. A more common and less expensive design that can be used to explore relevant genetic variations is the observational case-control study. Patients are enrolled based on their phenotype or drug response (i.e. efficacy, adverse events, toxicity). Since information based on the drugs they have used is often collected retrospectively, the majority of pharmacogenomic studies are appended to existing projects, for example to a clinical trial for a new drug or new treatment regime in which DNA has also been sampled. The ‘cases’ are the patients that have had an adverse drug reaction, experienced drug toxicity or those that did not improve significantly. The controls are the patients that did not experience an adverse drug reaction, did not experience drug toxicity or did improve on the drug regime.

A pharmacogenomic case-control study can also be designed based on an observational cohort study, such as the Pharmacogenomics of Asthma medication in Children with Anti-inflammatory effects (PACMAN)-cohort study. This Dutch cohort study recruited children that used asthma medication through community pharmacies. During a study visit, saliva for DNA analysis and phenotypic information (including health care visits in the past year and asthma symptoms in the past year) was collected. Cases and controls were subsequently assigned within the cohort based on the collected information. In the PACMAN cohort study, the cases were the children that had not responded well to asthma treatment (based on symptoms scores or exacerbations despite treatment in the past year), while controls were the children that had responded well to asthma treatment. A limitation of this type of design is recall bias. Since the patient has to report symptoms, exposure, and toxicity retrospectively, they might not always recall these events correctly. Furthermore, in comparison to a clinical trial, there is less monitoring and control, and issues such as non-adherence to treatment and dosage changes might lead to bias. However, this likely reflects standard clinical practice.

A third and upcoming study design is based on a DNA-biobank (See Background Paper 8.5) using data that is collected in a prospective or retrospective observational manner. An increasing number of medical centres collect biological specimens (including DNA samples) for research purposes and have these samples coupled to electronic health records. When this information also includes drug exposure and phenotype outcomes (i.e. adverse drug reactions), pharmacogenomics studies can be set up. An alternative strategy is to first identify cases and controls in the electronic health database and subsequently go back to the patients to obtain a DNA sample. An advantage of a biobank design is the large study populations available. Nevertheless, studies based on this design are limited by the information available in the electronic health records and in comparison to the other two designs, there is little control over the phenotype information that is collected. In addition, there are also large scale prospective longitudinal observational population cohort-studies which involve extensive phenotyping of individuals, but do not originate from medical centres with electronic health records (e.g. United Kingdom Biobank, Qatar Biobank). In these studies, phenotype information is tightly controlled and standardized.

Observational studies and biobank studies are generally used to assess (currently unknown) genetic/genomic variations, whereas RCTs are the current standard used to determine the clinical value of newly discovered gene-drug interactions before implementation in clinical practice. However, a RCT might not always be feasible, due to ethical or cost/resource limitations. In the case of cost or resource limitations, an adaptive trial design could be a
desirable alternative. An adaptive trial enables the researcher to implement prior knowledge (from observational studies or knowledge obtained during the early phase of the clinical trial itself) to optimize the remainder of the trial, which, for example, could lead to adjusted sample sizes.36

5.2 Defining Outcomes

A crucial step in pharmacogenomics research is defining the phenotype of interest or the outcome of the study. Many aspects of therapy response may be of interest as the outcome. Often pharmacogenomics studies focus on drug efficacy or toxicity; however, when addressing these issues, there is a wide variation in the phenotypes being studied, which makes comparability between studies difficult. It is also complicated to determine what defines a successful drug response outcome (differences in drug dosage, length of time that a patient is symptom-free, and different clinical measures of improvement), and study results may differ based on the definition of outcome.37 Hence, there is a need for the standardization of phenotypes of efficacy and adverse drug reactions.38

5.3 From candidate-gene approach to GWAS and whole-genome sequencing

Within the field of genomics, there are two approaches to DNA analysis: a hypothesis-driven approach (e.g. candidate-gene studies) and a data-driven approach (e.g. linkage studies, genome-wide association studies, whole-genome/exome-sequencing). In a candidate gene approach, the association between variations in selected genes and an outcome (i.e. disease susceptibility, therapy response) is studied. Genes are selected based on biological knowledge. For example, when studying drug-response, genes coding for proteins in the drug-metabolizing pathway might be selected as interesting candidates. This type of study is not designed to identify novel genomic areas that might be associated with the outcome, but rather to confirm a hypothesized association between a gene and the studied outcome.

In contrast, data-driven approaches including genome-wide association studies (GWAS), linkage studies and whole genome/exome sequencing are used to identify novel genomic variants. Genes are not selected based on a priori knowledge in this approach, but variation in the genome is studied in an unbiased context. Linkage studies have been used a great deal in the genetics field in order to genetically map diseases. In a linkage study, genetic markers are studied in families where a certain trait (e.g. disease) is inherited by several generations. The key is to identify a genomic region that is always inherited by the affected family members, but not inherited by the unaffected family members, and then narrow the genomic region down as much as possible. These studies are appropriate for the study of monogenetic traits. However, linkage studies are less suitable for drug response studies as it is rare to find a family with a well-characterized drug response. Compared to traditional genetic linkage studies, GWAS have higher statistical power to detect small to modest genetic effects. In a GWAS many common genetic variations across the entire genome are assessed in a large population of individuals to study whether any of the investigated variations are associated with a phenotype of interest (e.g. disease susceptibility, therapy response).39 The first GWAS was performed in 2005 on genetic variations associated with age-related macular degeneration,40 and the first pharmacogenomics GWAS was performed in 2008 on statin-induced myopathy. At present, over 1 300 GWAS have been performed (Figure 7.4.4), and a list of all the published GWAS performed can be found at the website of
the National Human Genome Research Institute.\(^1\) The majority of GWAS have focused mainly on the identification of disease susceptibility genes and far less on pharmacogenomics, yet GWAS are increasingly being used in that area.\(^2\) GWAS on treatment outcomes have mainly focused on drugs for which the dose needs to be individualized or on drugs to which a poor response has severe clinical consequences.\(^2\) One of the drawbacks of GWAS for pharmacogenomics is the large sample size requirements. Expected genetic effect sizes are often small, especially when studying outcomes such as rare adverse drug reactions, therefore it might be difficult to recruit large sets of patients. However, it seems that the genetic effect size for drug response is often higher than those reported for the genetic susceptibility for common complex diseases, and GWAS studies studying drug response with small sample sizes and highly significant findings do exist.\(^3,\)\(^4\) Nevertheless, large international research consortia are required to increase samples sizes and facilitate biomarker discovery and replication.

Figure 7.7.4: Number of GWAS published between 2005 and 2012

![Published GWAS reports, 2005-6/2012](image)


Furthermore, GWAS is less suitable in capturing rare variants, as the GWAS arrays are often designed to include mainly common genetic variants. Moreover, GWAS are very susceptible to finding false positives due to multiple testing.\(^5\) Correction for multiple testing is common practice in genomic research, however, it is complicated due to the existence of various methods that all have their own limitations.\(^6\) Traditional solutions (such as the Bonferroni correction) work well in settings were few genetic variants are studied, but may be too conservative for GWAS settings. Balancing the risk associated with finding false positives versus the risk that important genetic variants are missed (false negatives) remains an important challenge.
Whole genome sequencing would be more accurate in assessing rare variants, though it is still rather costly. The “1000 dollar genome” is expected to be realized in the near future\textsuperscript{47}, as sequencing costs are decreasing rapidly (Figure 7.4.5), yet currently it still costs over 1 000 US dollars to sequence the complete DNA sequence of an individual. A cheaper and promising alternative is whole-exome sequencing, whereby only the exonic regions of the genome are sequenced. Exonic regions code for functional proteins and comprise approximately 1\% of the human genome. An important advantage of this strategy is that rare variants with larger effects can be detected. However, current exome strategies do not cover all the exomes present in the human genome, nor can they detect structural variants or chromosomal rearrangements.\textsuperscript{48}

An innovative approach, which combines the hypothesis-driven and data-driven DNA analyses is the sequencing of 2 000 cancer-related genes of biopsies of cancer patients. In the Netherlands, three cancer centres are collaborating in the Center for Personalized Cancer Treatment (CPCT), and all patients with metastasized disease are asked to participate. Mutations in 2 000 cancer-related genes are being assessed in order to identify predictive and prognostic biomarkers.\textsuperscript{49}

**Figure 7.4.5: Decrease in costs per genome sequencing over time**

![Cost per Genome](http://www.genome.gov/sequencingcosts)

Source: National Human Genome Research Institute. Available at: [http://www.genome.gov/sequencingcosts](http://www.genome.gov/sequencingcosts) Accessed April 23, 2013\textsuperscript{50}

### 5.4 Other -omics technologies

Pharmacogenomics is only one of the many -omics technologies that have emerged. All of these technologies, to a greater or lesser extent, hold the promise of improving the prediction of disease, the prediction of drug response and the phenotyping of disease.\textsuperscript{44} Advances in these fields might provide valuable information about the biological pathways of disease and health and drug response variability. We will now address some of the more promising -omics technologies.
Pharmacoepigenomics is a relatively new field that focuses on environmentally-driven, inheritable variations in the DNA structure and its effect on drug response. As it seems, not only do variations in the sequence of DNA play a role in explaining heterogeneity to treatment response, but variations in the physical DNA structure also play a role. The structure of DNA is highly dynamic and regulates gene expression. Especially in cases where there is a strong observed inter-individual heterogeneity in treatment response, but no clear genomic association, epigenetic variations might be the missing link. Important epigenetic mechanisms include DNA methylation, posttranslational modifications of histone proteins and modulation of gene expression by noncoding RNAs. An example of pharmacoepigenomics is the observation that hypermethylation of the WRN promoter in colorectal tumours is associated with a clinical response to the drug irinotecan. Increased methylation of the gene promoter leads to the silencing of the gene and hypersensitivity to topoisomerase inhibitors and DNA-damaging agents such as irinotecan.

Transcriptomics investigates the transcriptome, the RNA transcripts produced by the genome, and the regulation of that process. In order to translate genetic information into proteins, DNA needs to be transcribed into RNA. Subsequently these RNA molecules can be used to produce proteins. However, a cell also produces RNA molecules that do not code for a protein (non-coding RNA), but still have regulatory functions within the cell. An important project which also involves transcriptomics is the Encyclopedia of DNA Elements (ENCODE) consortium. It focuses on the control of transcription by assessing regulatory pathways and regulatory DNA elements, and it aims to characterize the genome from a functional point of view. Current analyses include the study of 1640 genome-wide datasets from 147 different cell types, in order to gain more knowledge on the regulation of gene expression in health and disease.

Proteomics assesses the proteome of the cells, and the regulation and production of all the proteins in a cell. An alteration in the genome or transcriptome does not necessarily correlate with an alteration in a functional protein; therefore, proteomic profiling may sometimes be more accurate in predicting treatment response. Proteomics studies have, for example, assessed the influence of chemotherapeutics on the dynamics of protein response in cancer cells. Nevertheless, progress in proteomics has been limited thus far by labour-intensive procedures and lack of high-throughput arrays.

Metabonomics (or metabolomics) assesses the effect of a systematic change in a biological system caused by an intervention (such as drug administration or specialized nutrition). The assessment of the gut microbiome appears especially promising, since there is increasing knowledge about the metabolic interactions between individuals and gut bacteria and the effect on disease development, drug efficacy and adverse drug reactions.

5.5 Replication and validation of findings

To validate pharmacogenomic findings, replication studies in different cohorts are essential. Functional studies to assess the effect of the genetic variant on gene expression and protein function are crucial as well. However, this might be complicated by the variances in outcome definitions or phenotype descriptions. Furthermore, in order to profit optimally from identified risk SNPs (single nucleotide polymorphisms), we have to understand causative
relationships and underlying biological pathways\textsuperscript{38, 39} and to understand whether the identified SNP is a functional SNP or a surrogate marker.

Replication has become a standard practice in genomic research, stimulated by guidelines produced by journals on how to report genetic association studies.\textsuperscript{60} Nevertheless, translation of pharmacogenetic markers to clinical practice has been severely limited due to the low rate of successful replication. Failure to replicate could be due to the overestimation of the effect estimate and the use of an underpowered sample size, but it may also be due to the underestimation of the influence of environmental factors.

5.6 Future diagnostics: from genotype to diagnosis

With the rapid advances in -omics technologies and the emergence of new biological knowledge, it is becoming evident that the current way we classify diseases has become outdated.\textsuperscript{6} Diseases with distinct molecular causes are still classified as one disease (e.g. depression, lung cancer), while diseases that share a common molecular pathology are classified into a multitude of different diseases. With emerging biological knowledge, increased understanding of disease biology and the discovery of disease biomarkers, future clinical practice will increasingly diagnose and treat patients based on molecular disease mechanisms instead of, or in addition to, clinical symptoms. For research purposes there is a need to understand phenotypic extremes and endophenotypes (surrogate endpoints that reflect biological pathway activity). Furthermore, biomarker discoveries will most likely be more successful in patient groups with a homogenous molecular disease background. Patient selection before randomization in a clinical trial (‘enrichment’) to increase study power, to identify patients with a greater likelihood of having the event of interest, or patients that are more likely to benefit from the drug\textsuperscript{61}, will increasingly be based on –omics markers.\textsuperscript{62}

6. What European collaborations and EU-funded initiatives exist?

There are two main European networks in the field of pharmacogenomics: the European Society of Pharmacogenomics and Theranostics, which mainly focuses on the implementation of pharmacogenomics, and the European Research Network Pharmacogenetics/genomics, which mainly focuses on research. Additionally, The European Personalised Medicine Association (EPEMED) is a not-for-profit organisation that aims to bring global forces in stratified medicine together in order to harmonize stratified medicine development and implementation across Europe, with a focus on diagnostics. It aims to represent members from academia and industry, as well as patient groups and professional service firms.\textsuperscript{63} Furthermore, various large international Europe-wide pharmacogenomics studies are emerging (See Table 7.4.2).
Table 7.4.2: EU-funded Initiatives and European consortia on stratified medicine

<table>
<thead>
<tr>
<th>Study acronym</th>
<th>Topic of investigation</th>
<th>Funding</th>
</tr>
</thead>
<tbody>
<tr>
<td>EU-PACT</td>
<td>Pharmacogenomics of anti-coagulant therapy</td>
<td>EU-FP7*</td>
</tr>
<tr>
<td>FLIP</td>
<td>Progression of non-alcoholic fatty liver disease and the validation of diagnostic and prognostic markers</td>
<td>EU-FP7</td>
</tr>
<tr>
<td>TINN</td>
<td>Efficacy and safety of anti-infectious drugs in neonates</td>
<td>EU-FP7</td>
</tr>
<tr>
<td>EuroTARGET</td>
<td>Targeted therapy in renal cell cancer</td>
<td>EU-FP7</td>
</tr>
<tr>
<td>BIOSTAT-CHF</td>
<td>Pharmacogenomics and biomarker project on chronic heart failure</td>
<td>EU-FP7</td>
</tr>
<tr>
<td>MoMoTx</td>
<td>Diagnostics in kidney transplant patients</td>
<td>EU INTEREG IVa</td>
</tr>
<tr>
<td>U-BIOPRED</td>
<td>Biomarkers of severe asthma</td>
<td>IMI**</td>
</tr>
<tr>
<td>IMI-DIRECT</td>
<td>Patient stratification in type 2 diabetes</td>
<td>IMI</td>
</tr>
<tr>
<td>IMI-SUMMIT</td>
<td>Micro- and macro-vascular hard endpoints for innovative diabetes tools</td>
<td>IMI</td>
</tr>
<tr>
<td>PADRE</td>
<td>Pharmacogenomics of antidepressant response prediction</td>
<td>EU-funded but through national funding authorities</td>
</tr>
<tr>
<td>ITCH</td>
<td>International Consortium on Drug-induced skin and hypersensitivity</td>
<td>Not EU funded</td>
</tr>
<tr>
<td>iDILIC</td>
<td>International Consortium on Pharmacogenomics of Drug-induced liver injury</td>
<td>Not EU funded</td>
</tr>
</tbody>
</table>

* EU-FP7: European Union’s 7th Framework program  
** IMI: public-private Innovative Medicines Initiative

7. Genomics initiatives in low resource settings

Genomics initiatives have started to emerge in some low- and middle-income countries such as Mexico\(^64\), India\(^65\) and Gambia\(^66\); nevertheless, for the majority of low- and middle-income countries, stratified medicine seems to be far out of reach.\(^67\) At present, there is a lack of technical and financial resources and infrastructure.

In 2005, a report from the Royal Society on stratified medicine\(^68\) advocated the development and use of simple phenotypic tests in order to screen common genetic defects in order to address medical needs in those countries. This idea is demonstrated in the case of glucose-6-phosphate dehydrogenase (G6PD) deficiency, this disorder is common in malaria endemic regions and causes severe anaemia after the use of (among other drugs) the anti-malarial agent, primaquine. The gold standard in assessing the G6PD status of an individual is a spectrophotometric assay of red cell G6PD content, but this requires a laboratory setting.\(^69\) Simple enzyme-based UV tests (‘fluorescent spot test’), which can be performed in the field, are available, but they are not widely being used. According to a recent meeting report of the WHO Malaria Policy Advisory Committee, implementation of such tests requires quality control of the field laboratory results, as well as a cold chain to transport and store reagents.\(^70\) New point-of-care tests are currently under development.

In addition to G6PD, various other genetic factors are thought to influence the effectiveness of anti-malarial agents, but there is a lack of pharmacogenetic data in low- and middle-income countries, where they bear a disproportionate disease burden.\(^71\) In order to gain knowledge, collaborations between parasitologists, national public health programmes and genetic researchers should be promoted.\(^71\) Dried blood spots collected for efficacy studies
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could be used for pharmacogenetic studies as well, as long as consent is obtained for retrospective DNA testing.

We have to bear in mind, however, that the use of genetic testing might not be cost-effective in low- and middle-income countries where basic health care is limited and appropriate drugs are not always available. An alternative and novel approach to disease profiling is the recently developed Xpert MTB/RIF® to diagnose tuberculosis (TB) and drug-resistant TB on a molecular basis. It is a rapid test, taking less than two hours, that assesses the tuberculosis genome in patient sputum samples with high sensitivity and specificity. However, a recent cost and affordability analysis showed that the test is currently not financially viable in low-income countries as long as funding for tuberculosis and cost reductions are not increased. Nevertheless, after a successful South-African pilot-study, the technology is currently being rolled out nationwide by the South African National Department of Health. Xpert platforms will be placed in all laboratories in nine designated high case-load districts and in all other existing TB laboratories. It is estimated that the technology will substantially increase the number of TB diagnoses, yet will also increase annual costs for TB diagnostics and treatment. (See Background Paper Chapter 6.8 on Tuberculosis)

So far, most pharmacogenomics research has focused on Caucasians. However, clinically relevant SNPs might be present in non-Caucasian populations, but be virtually absent in Caucasians; a good example of this being the HLA-B*1502 allele. Individuals with this allele have a higher risk for severe cutaneous allergic reactions caused by anti-epileptic drugs. The allele is more prevalent in populations with Asian ancestry (10-15%) compared to Caucasians (1-2%). The Pharmacogenetics for Every Nation Initiative (PGENI) was developed to support pharmacogenomic research in low resource settings by developing and integrating local risk data. This USA-based non-profit organization aims to sample 500 individuals from every ethnic group that represents 1% or more of the population in 104 low- and middle-income countries. Another important initiative is the China Kadoori Biobank which has collected data from over half a million individuals from ten geographically defined Chinese regions. The researchers goal is to follow the individual’s health for at least two decades, with a wide range of measurements have been performed, including the collection of blood and DNA.

Particularly in low resource settings, (pharmaco)genomic approaches may hold promise in addressing their limited health resources as efficiently as possible. The focus here should lie on a better use of existing medicines.

8. Challenges for implementation

In order to successfully bring stratified medicine to the clinic setting, there are several challenges to overcome, including the following: pricing and reimbursement, assessing its clinical value, regulation of products, legal and ethical issues, dealing with orphan drugs and patients, addressing the need for a well-organised technology infrastructure and public and professional training.
8.1 Pricing and reimbursement

In recent years, stratified medicine (drugs and associated biomarkers), also known as co-dependent technologies or ‘joint products’ or ‘therapeutics with companion diagnostics’, has gained more and more relevance, which poses certain challenges to the pricing and reimbursement authorities. Three main points should be highlighted:

1. In Europe, most stratified medicine belongs to a group of high-cost medicines for which public funding – either through hospital budgets or through the outpatient reimbursement sector – can be a challenge for public authorities (See Background Paper 8.2 on Pricing and Reimbursement). One well-known example is trastuzumab, for which European countries pay, on average, €600 per 150 mg powder vial (See Figure 7.4.6). Prices for medical tests, such as the HER2-positive breast cancer tests (FISH test), are not publicly available and can be freely set by the manufactures. According to a study by the Institute for Prospective Technological Studies, costs for the FISH-test (including material and personnel costs) varied between €220 in the United Kingdom to €495 in the Netherlands in 2006.

2. Stratified medicine combines the use of medical devices, such as tests, with medicines and new reimbursement assessment procedures – often in the course of health technology assessments – that take into account the whole treatment package that needs to be developed. In a benchmarking report examining factors that support or hinder market access to stratified medicine in reimbursement systems in European countries, countries were ranked as supportive (e.g. Germany, the United Kingdom and France) when reimbursement systems for the diagnostic and therapeutic were combined. However, for other countries (e.g. Netherlands, Finland and Norway), no clear pathways for evaluation and funding of stratified medicine were identified.

3. Stratified medicine is at the juncture of the inpatient and the outpatient sectors, which is especially relevant with regard to funding. A study undertaken in the framework of the EMINet (European Medicines Information Network; to support policy makers of the network of Competent Authorities of Pricing and Reimbursement (CAPR)) surveyed funding models and pricing practices for the ‘treatment package’ of trastuzumab and its accompanying diagnostics in 27 European countries, as an example of personalised medicine. The results showed split funding in several countries; medicine expenses were funded by third-party payers and the tests were paid for by the hospitals, which further increased the pressure on hospital budgets. Furthermore, pharmacogenomic tests were only reimbursed when clinical utility of the test was established. However, there is little consensus on what evidence is needed for tests to have sufficient clinical value. Some countries are countering this gap by establishing prescribing guidelines which consider both the medical device and the medicine or interdisciplinary committees with representatives from hospitals and third party payers.
Figure 7.4.6: List prices of one 150 mg vial of trastuzumab at unit ex-factory price level in EURO in thirteen European countries, 2005 and 2011.

AT = Austria, BE = Belgium, DE = Germany, DK = Denmark, EL = Greece, ES = Spain, FI = Finland, FR = France, IS = Iceland, IT = Italy, NL = Netherlands, NO = Norway, SE = Sweden, UK = United Kingdom. (Source for abbreviations: http://publications.europa.eu/code/en/en-370100.htm)

UK: price paid by the National Health Service
Prices as of December 2005 and June 2011
Prices in Non-Euro-countries were converted with the corresponding monthly exchange rate as published by the European Central Bank.
http://www.oenb.at/de/stat_melders/datenangebot/zinssaetze/wechselkurse/wechselkurse.jsp

Source: Pharma Price Information (PPI) service. Gesundheit Österreich GmbH (Austrian Health Institute). 2012.78

8.2 Assessing clinical value

The assessment of the clinical value of a test or a marker demands the development of a strategy for translational research in which evidence is gathered over time in order to allow the incorporation of various tests into health care practice within a certain time frame, while also assessing clinical utility and cost-effectiveness. Gathering evidence needs to take place in several phases, similar to the phases of pharmacological research. A four phase framework for translational research of genomic medicine was proposed by Khoury and colleagues.84

Phase 1 seeks to move a basic genome-based discovery into a health application: an example is the construction of a genomic profile that predicts individual reactions to drugs. Phase 2 would lead to the development of evidence-based guidelines. A clinical trial that shows that the adapting treatment to the genomic profile in a large group of study participants is effective in avoiding side effects would fit into this phase. Phase 3 attempts to move evidence-based guidelines into health practice. An implementation project to ensure that all people in an entire country to whom a certain drug is being prescribed are first tested using the genomic profile to determine their risk of side effects would fit in phase 3. Phase 4 seeks to evaluate the ‘real world’ health outcomes of a genomic application in practice. The evaluation of the occurrence of side effects to show that fewer people are affected after the implementation of the genomic profile would be the phase 4 study of our example. It is estimated that no more than 3% of published genomics research focuses on phase 2 and
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beyond\textsuperscript{84}, implying that evidence-based guidelines are rare in the field of genomics. An additional example of the different phases of translation is given in Table 7.4.3 for HER2 testing and trastuzumab treatment.

Nonetheless, for cost, resource use issues (pharmaceutical industry might not be interested in financing off-patent products) and ethical reasons (strong observational evidence of a high risk of severe adverse events in patient subgroups) clinical trials will not be feasible for every newly discovered biomarker-drug interaction. Yet the replication of findings obtained in observational studies can be difficult, therefore strict guidelines are necessary to define which evidence is required before a test can be implemented in clinical practice and whether a clinical trial is needed. The following factors should be taken into account:\textsuperscript{85}

- Replication of findings in distinct study populations with diverse geographical backgrounds and genetic ancestries
- Severity of clinical event
- Likelihood of clinical event
- The prevalence of the marker across distinct populations (in the case of genomic biomarkers)
- Cost-effectiveness
- Availability of clinical infrastructure, including a simple cost-effective clinical assay

In addition, the ease of implementation in a suitable clinical setting needs to be considered. Will the biological samples need special handling conditions? Is the analytical test robust in different (e.g. environmental) settings? Will the analytical technology be readily implemented? Does the analysis require additional skilled personnel or can standard clinic or clinical-lab staff perform it?

Table 7.4.2: Phases of translation with trastuzumab and HER2 testing as example

<table>
<thead>
<tr>
<th>Phase</th>
<th>Description of phase</th>
<th>Research question or activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 1</td>
<td>Discovery to health application</td>
<td>How do cancer cells with high levels of the HER2 protein respond to trastuzumab therapy?</td>
</tr>
<tr>
<td>Phase 2</td>
<td>Development of evidence-based guideline</td>
<td>Develop guideline specifying to whom HER2 testing is offered and to whom trastuzumab is prescribed in cancer clinic in a research setting</td>
</tr>
<tr>
<td>Phase 3</td>
<td>Move guideline into health practice</td>
<td>Instruct oncologists nationwide to use guideline</td>
</tr>
</tbody>
</table>

Source: Vijverberg SJ, Pieters T, Cornel MC. Ethical and social issues in pharmacogenomics testing. Curr Pharm Des 2010;16(2):245-52.\textsuperscript{86}
8.3 Regulation of products

Regulatory authorities play an important role in the implementation of stratified medicine. However, a 2007 meeting report of the Academy of Medical Sciences on optimizing stratified medicine research and development outlined important pre- and post-approval barriers. According to the report, drugs and diagnostics are ideally developed simultaneously and stratification of patients is taken into account during the drug development process, market authorization process and reimbursement procedures. However, introducing stratification prior to drug registration is complicated due to the different regulatory frameworks for diagnostics and therapeutics in the EU, which is in contrast to the United States where diagnostic and therapeutic approval applications to the FDA can be made simultaneously. The European Commission has recently submitted a proposal for a new regulation to replace the current Directive 98/79/EC on in vitro medical devices, which includes clinical genetic tests. Other regulatory guidelines and reimbursement procedures should also be adapted. There is a need to align regulatory processes between different regulatory agencies. Furthermore, the lack of consensus on what evidence is needed to demonstrate clinical utility and analytical validity of a diagnostic also hampers implementation, as well as the current gold standard of the RCT (See section on study design).

Current regulatory guidelines on the role of pharmacogenetics in evaluating drug pharmacokinetics differ on covered drug development phases, recommendation for DNA storage and if a pharmacogenetics-related pharmacokinetics study is required or recommended. Furthermore, the available regulatory guidelines seem primarily relevant for drugs under development and not for registered drugs.

Pharmaceutical companies may have relatively little interest in assessing stratification post drug approval, since this might reduce their return on investment, such as the case may be when the use of the drug is shifted from an initial broad indication to a narrow, yet highly effective, indication. However, flexibility in pricing could overcome this hurdle. From a societal point of view, the inclusion of stratification on the drug label (testing prior to prescription) might lead to the emergence of many new, small population subgroups, some with rare genotypes (see section on ‘emergence of orphan populations’).

In order to enhance the understanding of the regulatory significance of genomic data, the FDA initiated the Voluntary Genomic Data Submissions (VGDS) program in 2004 to allow sponsors (industry, researchers) to submit exploratory genomic data voluntarily, without immediate regulatory impact. In order to expand the program to non-genomic biomarkers, the submissions have been renamed Voluntary Exploratory Data Submissions. This provides the opportunity to discuss exploratory data on genomic and non-genomic biomarkers between sponsors and regulators without the submission of an investigational new drug application, a new drug application or biologics license application. Joint FDA-EMA VXDS meetings have taken place in order to generate international consensus on the opportunities and limitations of genomic and non-genomic biomarker data in drug development.

The FDA and the EMA both have a qualification process for drug development tools, which include non-genomic biomarkers. Plasma fibrinogen is one of the first biomarkers that is currently progressing through the final stages of the new FDA DDT qualification review. Increased fibrinogen levels are thought to be a marker of COPD patients at risk for hospitalization and death.
8.4 Legal and ethical issues

The new genomic era requires large numbers of participants in order to identify small risk effects of common gene variants. Biobanks have emerged to store biological specimens and genetic information, and data sharing is considered to be an essential part of the current genomic research process. This raises new ethical and legal issues, concerning consent, ownership and liability, for example.86

Participants in genomic studies have to give ‘informed consent’ to their participation in the study and the use of their DNA samples. The text of the consent form also usually includes possible implications for the research participant concerning issues such as privacy, confidentiality and re-contacting. However, due to extensive data sharing, the emergence of large-scale research platforms and the unique fingerprint nature of DNA, the validity of privacy and confidentiality assertions are being challenged. When the genome of the discoverer of the double helix, Dr James Watson, was sequenced, he agreed to release it to public databases, except for the information about the gene apolipoprotein E. This gene is known for its association with late onset Alzheimer disease. However, even Dr Watson did not foresee that his genotype for apolipoprotein E could still be imputed with more than 99% certainty based on his other genetic information.85 Furthermore, keeping genomic information in complete anonymity is not technically feasible, nor desirable, should the participant wish to withdraw from the study. Genomic data obtained from a research participant may also hold information about family members who did not consent. In addition, a better understanding of genomic information might bring clinical relevant information that was not the aim of the primary study (‘ancillary or incidental findings’ – the incidentalome86). For example, it has been shown that some genetic variants associated with drug response can be associated with disease predispositions. How to handle the feedback of this kind of additional information while still protecting the ‘right not to know’ remains a challenge.87

In the context of privacy and confidentiality, the concept of ownership has also been much discussed: who owns the genetic information of a study participant and which parties should have access to this information? Most European countries have adopted genetic anti-discrimination legislation in order to prevent misuse of genetic information by employers or insurers. However, there is an ongoing debate as to how well these anti-discrimination laws actually protect the privacy and confidentiality of individuals. A 2008 study by Van Hoyweghen and colleagues showed that Belgian insurance companies still used genetic test results or genetic information derived from physician records or insurance questionnaires despite the existence of genetic anti-discrimination legislation.86 This practice was mainly due to ignorance, confusion and misunderstanding, but was also the result of the lack of clear legal definitions for ‘genetic data’ and ‘genetic tests’.

Implementation of pharmacogenomics in clinical practice requires that health care providers are prepared for the sometimes new, and often complex legal issues that the introduction of a new technology brings with it, for example, concerning liability. A pharmacist has a professional duty to assess whether a certain drug type and dose is suitable for a patient. When an adverse drug reaction, which could have been avoided by the use of a pharmacogenomic test, occurs in a patient, the pharmacist could be liable, or in other words legally responsible. Take, for example, coumarin anticoagulants. A major side effect of coumarin anticoagulants is severe bleeding, with reported incidences of 1.5 to 5.0 per 100
patients a year. It has been shown that individuals who have variant alleles of the VKORC1 and CYP2C9 genotypes are at an especially increased risk of drug-induced bleeding. Therefore, if pharmacogenetic testing for VKORC1 and CYP2C9 were to be made standard care, and a pharmacist was to dispense warfarin in the absence of testing, the pharmacist could be held liable if drug-induced bleeding occurred. However, the extent of liability depends on accepted standards of care, as formulated in guidelines, and it is unclear whether any pharmacogenomics application is currently considered to be ‘standard care’. Although there are pharmacogenomics tests used in clinical care, clinical practice guidelines are rare, and labelling content is limited. The tests that are clinically available are mainly restricted to the oncology, HIV, psychiatry and the cardiovascular field.

8.5 The emergence of orphan populations

There is some concern that stratified medicine may lead to many new, small subgroups of disease populations, some with rare genotypes. Pharmaceutical companies might find it unattractive to invest in drug development for these small subgroups, and will instead focus on the most prevalent genotypes. Patients with the rare genotype groups would then be ‘orphaned’ by the international therapeutic drug market. Drugs for rare diseases are known as ‘orphan drugs’ (See Background Paper 6.19 on Rare Diseases). In the Netherlands, the Dutch Steering Committee for Orphan Drugs launched an initiative in January 2009 in order to encourage translation in the field of rare diseases by supporting companies in submitting an Orphan Designation Dossier (ODD) to the EMA. Similar public private partnerships are needed to stimulate research on rare genotypes. On the other hand, stratified medicine might lead to a better use of existing medications. Drugs with severe, adverse drug reactions might still be safely used in patients with a favourable genetic profile, and therefore be kept on the market, a good example being the anti-HIV drug abacavir (Box 7.4.2: the abacavir case).

8.6 Technology infrastructure

Health information technology guides the exchange of medical information between patients and providers. For a successful implementation of stratified medicine, a well-structured health information technology infrastructure is required to enable standardized data collection and to link pharmacogenomics data to clinical information systems in order to facilitate surveillance and guide treatment decisions. In the Netherlands, the Pharmacogenetics Working Party of the Royal Dutch Society for the Advancement of Pharmacy is currently working to implement pharmacogenomics in their automated medication control database in order to link pharmacogenomics test results to therapeutic recommendations. These databases are used by the majority of general practitioners and community and hospital pharmacists in the Netherlands. However, a major limitation is the lack of genotyping data and there is limited evidence to justify prospective pharmacogenomic testing. Furthermore, the infrastructure for genotyping is only available in a subset of centres. In order to bring stratified medicine successfully to the clinic and pharmacy counter, it is necessary to develop guidelines, register unfavourable gene variants, and implement signalling systems that raise an alarm when drugs are dispensed for which pharmacogenomics tests are required.
8.7 Education and training

The requirement of genomics or biomarker testing before initiating drug treatment is already standard practice for some drugs (e.g. abacavir and trastuzumab) and will only increase over the coming years. Nonetheless, a recent study of more than 10,000 American physicians showed that less than a third had received education or training in pharmacogenomics. Health care providers, including physicians, pharmacists and nurses, should be better prepared for clinical decision making by having adequate knowledge about the medicines for which the patient should be tested. They need to be trained to interpret (pharmacogenomic) genomic data and test outcomes and to learn how to make clinical decisions based on the data and to discuss genetic risks and stratified medicine with patients. Education should not only be part of the basic training of health care professionals, but should also be part of postgraduate courses to provide continuous training on new developments. Several initiatives are emerging; the American Medical Association (AMA) has developed a brochure for physicians and other health care providers to improve their basic knowledge on pharmacogenomics. The United Kingdom Centre for Pharmacy Postgraduate Education has developed an online learning course for pharmacists, and pharmacogenomics is increasingly becoming part of the curriculum of pharmacy students. Furthermore, pharmacogenomics is also included in the EU2P training program (the European IMI Education and Training e-learning Master and PhD programme), funded by the European Commission and the pharmaceutical industry. Another EU initiative is the ‘Fighting Drug Failure’, of the Marie Curie Initial Training Network that focuses on pharmacogenomics. It is a three year PhD programme for selected international junior and senior researchers.

Although pharmacists play a pivotal role in the implementation of pharmacogenomics, educational tools should also be developed for other health care providers. There is a need for standardised courses: educational courses for a broad range of health-care professionals (clinicians, nurses, health care provider managers) in order to gain general knowledge and promote implementation of stratified medicine in clinical practice, as well as in-depth educational courses for researchers, clinical specialists and pharmacists. Furthermore, database designers, biostatisticians and informaticians need to be trained in order to optimize database building and data analysis. The public needs to be educated in order to understand the possibilities and limitations of stratified medicine to prevent misplaced anxieties or expectations and the development of mobile health care applications might play a role in doing so.

9. Identified gaps and recommendations for research and policy

Stratified medicine will have a major impact on the health care system by stratifying patients before initial treatment into groups of responders and non-responders, or patients with a high chance of experiencing drug toxicity and patients with a low chance of experiencing drug toxicity. It holds strong promise for enhancing drug safety and efficiency (of existing drugs), as well as for the development of new drugs, drug targets and diagnostics. Despite rapid technological developments and emerging collaborations, several gaps related to the development, translation and implementation of knowledge remain.
Establishing a funded European research network

In contrast to the United States (www.pharmgkb.org), there is no funded research network for pharmacogenetics in Europe. It would be beneficial to have a funded European research network that can be the voice of the research community. This network could greatly assist the European Union in identifying opportunities in research, strengthening collaborations within Europe, as well as playing a role in standardization processes (for example phenotype definitions) and organizing educational and scientific conferences.

Safer use of existing medicines is underserved

The main focus of stratified medicine lies in the development of new drugs, drug targets and diagnostics. This focus is also reflected in the guidelines of the various regulatory agencies for pharmacogenomics methodologies used in assessing drug pharmacokinetics, which primarily concentrate on drugs that are currently under development. In addition, pharmaceutical companies will probably be less interested in assessing stratified medicine post drug approval due to pricing inflexibility and possible market loss. However, in both low and in high resource settings, pharmacogenomics approaches to existing drugs may hold promise for addressing health resources optimally. Pan-industry studies to address stratified medicine with approved drugs should be stimulated, as should academia-initiated studies in this area.

The effect of non-genomic factors influencing treatment response should not be underestimated. So far, a large part of variability in treatment response cannot be explained by genomic variations. Patient characteristics (such as age, gender, severity of disease), gene-environment interactions, patient compliance, epigenomic regulation and protein modification might also play an important role and should not be underestimated. Multi-dimensional analyses in which biomarkers generated from different technologies (transcriptomics, epigenomics, metabonomics) are combined with clinical parameters might provide more insight in the pathogenesis, development and treatment response of multifactorial diseases.

Need for a European catalogue of pharmacogenomic dataset and harmonization program

To validate pharmacogenomic findings, replication studies using different cohorts and harmonization of outcomes is essential. A European pharmacogenomic database (to be extended to a global database) with a comprehensive inventory of available phenotypes, treatment data and other variables, as well as biological specimens, is lacking. Such a database could make the replication of findings easier, leading to more international collaborations and it could also identify those phenotypes/drugs where more data gathering is needed. Altogether this will assist in the collection of more evidence, and, therefore, to an increased chance of clinical implementation. An IT platform that will allow for data sharing is therefore essential.

Current regulatory guidelines and reimbursement procedures hamper implementation

The regulatory frameworks of the FDA and EMA differ concerning applications of stratified medicine and mainly focus on drugs under development. There is a need to harmonize both regulatory processes between the various regulatory agencies, and also on the evidence needed for clinical utility. A randomized clinical trial might not always be feasible due to
ethical considerations, a lack of resources or small populations. Clear guidelines are needed to assess when a RCT is necessary to test a stratified medicine approach. Furthermore, an adaptive trial design which enables the researcher to implement prior knowledge to optimize the remainder of the trial, might be a cheaper and faster alternative to testing observational findings. Cost-effectiveness studies are essential in assessing clinical validity. In addition, product pricing frameworks should be reassessed in order to stimulate research in the commercial sector on stratified medicine for registered drugs. Collecting and banking genomic samples should become an integrative part of pharmaceutical, academic and/or government funded RCT’s.

Stratified medicine in low resource settings is rare

A number of genomics initiatives are emerging in low resource settings; however, stratified medicine approaches are rare. Especially in countries where resources are limited, stratified medicine might be very successful in ensuring that limited health care resources are used as efficiently as possible. Implementation of pharmacogenomics strategies of existing drugs in low- and middle-income countries should be encouraged, taking their limited resources into account. Furthermore, pharmacogenomics research in patients with different backgrounds should be stimulated. This is also relevant to the situation in Europe, based on the large changes in migration during the past decade.

Stratified medicine in vulnerable groups should be stimulated

Research should be funded to allow biomarker based prescribing during pregnancy and childhood. The effect of distinct (genomic and non-genomic) predictors of therapy response might be different in these subgroups and should therefore not be extrapolated from pharmacogenetic-guided dosing algorithms developed for (non-pregnant) adults.

Clinical added value should be assessed

Consensus should be reached on what evidence is needed for tests to have sufficient clinical value. The assessment of the added clinical value of a test or a marker demands the development of a framework in which clinical utility and cost-effectiveness are assessed and compared to current clinical practice.

Barriers for implementation should be diminished

In order to prepare health care providers for clinical decision making based on stratified medicine, there is a need for coordinated education and training programs, educational courses for a broad range of health-care professionals and in-depth educational courses for researchers, clinical specialists and pharmacists. Workshops involving both pathology services and medicine therapy experts are necessary in order to guide the selection of those medicines that require testing, as well as how test outcomes should be interpreted and how dosages should be altered. Furthermore, database designers, biostatisticians and informaticians need to be trained in order to optimise database building and data analysis, and the public needs to be educated in order to understand the possibilities and limitations of stratified medicine.
Ethical, legal and social implications of stratified medicine should be further investigated

The new genomic era brings along new ethical and social issues concerning genomic data sharing, consent, ownership and liability. Furthermore, the level of protection by genetic anti-discrimination laws and the societally acceptable costs of innovative drug therapies should be investigated. Moreover, there is a lack of knowledge on the behavioural impact of genomics-based risk assessments. All these issues should be further studied in order to guide the implementation of stratified medicine in global health.

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