Pharmacogenetics, Controversies and New Forms of Service Delivery in Autoimmune Diseases, Acute Lymphoblastic Leukaemia and Non-Small-Cell Lung Cancer

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ABSTRACT

Pharmacogenetics (PGx) and personalised medicine are new disciplines that, gathering the existing knowledge about the genetic and phenotypic factors that underpin drug response, aim to deliver more targeted therapies that avoid the existing problems of adverse drug reactions or lack of drug efficacy. PGx and personalised medicine imply a shift in the way drugs are prescribed, as they require introducing diagnostic tools and implementing pre-screening mechanisms that assess patients' susceptibility to new or existing drugs. The direct benefit is an improvement in drug safety and/or efficacy.

However, neither pharmacogenetics nor personalised medicine, are widely used in clinical practice. Both technologies face a number of controversies that hamper their widespread use in clinical practice. This thesis investigates the scientific; technological; social; economic; regulatory and ethical implications of PGx and personalised medicine, to understand the enablers and barriers that drive the process of technology diffusion in three conditions: autoimmune diseases, acute lymphoblastic leukaemia and non-small cell lung cancer.

The thesis uses concepts of the sociology of science and a qualitative approach, to explore the arguments for and against the use of the technology by different actors (pharmaceutical and biotechnology companies, researchers, clinicians, regulators and patient organisations). The core of this analysis lies in the understanding of how, diagnostic testing (TPMT testing in the case of autoimmune diseases, acute lymphoblastic leukaemia, and EGFR testing in the case of non-small-cell lung cancer) may affect the existing drug development and service delivery mechanisms, with a particular focus on the user-producer interactions and feedback mechanisms that underpin diffusion of medical innovations and technological change in medicine.

The thesis concludes by identifying gaps in knowledge and common issues among TPMT and EGFR testing, which might be used, in the future, to inform policy on how to improve PGx service delivery through a public Health System such as the NHS.

DECLARATION

No portion of the work referred to in the thesis has been submitted in support of an application for another degree or qualification of this or any other university or other institute of learning.

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LIST OF ABBREVIATIONS

6-MP: 6-Mercaptopurine

6-TG: 6-Thioguanine

ABPI: The Association of the British Pharmaceutical Industry

ADR: Adverse Drug Reaction

AGEMED: Agencia Española de Medicamentos y Productos Sanitarios (Spanish drug approval and regulatory agency)

AGGR: UK DoH Advisory Group on Genetics Research

ALL: Acute Lymphoblastic Leukaemia

AZA: Azathioprine

BGMA: The British Generic Manufacturers Association

BMA: British Medical Association

BSC: Basic Standard Care

CD: Crohn's disease

CHMP: EMEA Committee for Medicinal Products for Human Use

CPMP: EMEA Committee for Proprietary Medicinal Products

CTSU: Clinical Trial Service Unit

DoH: (UK) Department of Health

ISEL trial: Iressa® Survival Evaluation in Lung cancer trial

ECEDMD: EC European Diagnostic Medical Devices

EEA-EFTA: European Economic Area – European Free Trade Association

EGFR: Epidermal Growth Factor Receptor

EMEA: European Medicines Evaluation Agency

ERG: Erlotinib Review Group

FDA: Food and Drug Administration

FISH: Fluorescence In-Situ Hibridation

FN: Febrile neutropenia

GMC: General Medical Council

GSL: (pharmaceuticals) General Sales List

HOM: Hospital-only medicines

HPLC: High Performance Liquid Chromatography

IBD: Inflammatory Bowel Disease

IHC: Immunohistochemistry

IP: Intellectual Property

IPRs: Intellectual Property Rights

IVD: In Vitro Diagnostics

LDTs: Laboratory Developed Tests

MHRA: UK Medicines and Health care Regulatory Agency

MRC: Medical Research Council

MRD: Minimal Residual Disease

MRFG: EMEA Mutual Recognition Facilitating Group

MS: Mass Spectroscopy

MTHFR: Methylenetetrahydrofolate reductase

NHS: National Health Service

NICE: National Institute of Clinical Excellence

NSCLC: Non-Small-Cell Lung Cancer

NHSBSA: NHS Business Service Authority

PCR: Polymerase Chain Reaction

PCT: Patent Cooperation Treaty

PGx: Pharmacogenetics

PGWP: EMEA PGx Working Party (later PGx Expert Group)

PMDA: (Japanese) Pharmaceuticals and Medical Devices Agency

QALYs: Quality-Adjusted Life-Years

RA: Rheumatoid Arthritis

SNP: Single Nucleotide Polymorphism

SNS: Sistema Nacional de Salud (Spanish National Health Service)

TK: Tyrosine Kinase

TNF-α: Tumour necrosis factor

TPMT: Thiopurine Methyl Transferase

UC: Ulcerative Colitis

UKLCC: United Kingdom Lung Cancer Coalition

VDSC: FDA Voluntary Data Submission Scheme

GLOSSARY

Adverse Drug Reaction (ADR): side effect from a medicine.

Alleles: alternative forms of each of the pairs of a gene (each gene is formed by two alleles). During the thesis we refer to the allele for high levels of TPMT (H) and the allele for low levels of TPMT (L). The combination of this two alleles leads to three different genetic variations: TPMT ^{HH}, TPMT ^{LL} and TPMT ^{HL}.

Analytical validity (of a diagnostic test): accuracy and reliability of a diagnostic test.

Azathioprine (AZA): drug that suppresses the immune system and is used in organ transplantation and to treat autoimmune diseases.

Biologics (drugs): substances produced by a living organism. They can be molecules used as therapeutic agents as ß-interferon or vaccines.

Biomarker: quantifiable measurements that define what is "normal", providing a frame of reference to define what is "abnormal". In cancer, biomarkers exist in different forms, from the images obtained through scanners to specific molecules like the prostate-specific antigen (PSA) for diagnosing prostate cancer, or genetic alterations or gene polymorphisms.

BR21 trial: clinical trial coordinated by OSI pharmaceuticals, which studied the response to Tarceva® (Erlotinib) *vs*. placebo for the second- or third-line treatment of patients with advanced NSCLC.

Cytokines: large family of proteins, excreted by cells from the immune system and which function involves carrying signals locally between the cells. Cytokines can also be obtained in the laboratory by recombinant technologies and be used to treat some diseases like some types of cancer.

Cytostatic agents: components (including drugs) that prevent the proliferation of cells, in opposition to cytolitic agents that kill the cells.

Clinical Utility (of a drug, test or medical device): concept used in medicine that lacks of an agreed formal definition but which usually refers to clinical together with economic effectiveness.

Clinical Validity (of a diagnostic test): accuracy with which a test can predict the presence of a phenotype or a genotype, which can later on be associated with diseases diagnosis or drug susceptibility.

Epidermal Growth Factor Receptor (EGFR): receptor placed in the surface of the cells that is activated by specific ligands which include the epidermal growth factor. The EGFR is linked to some proteins denominated tyrpsine kinases (TK). When the binding of the ligand and the receptor occurs, these TK get activated and trigger a cascade of biochemical reactions inside the cell. Polymorphisms in the EGFR receptor have been associated with a number of cancers, lung cancer among them.

Genotype: genetic constitution of a cell. The genotype usually makes reference to a specific character.

Genotyping: Deciphering of specific genotypes through DNA technologies.

Health System: Organisations, institutions and resources whose primary objective is improving the health of the population.

Hemogram: blood test.

Heterozygous: term used to designate an individual with a gene which alleles are different. In the case of TPMT, there is one heterozygous profile: $TPMT^{HL}$

High Performance Liquid Chromatography (HPLC): technology used in biochemistry and analytical chemistry to separate, identify and quantify compounds within a mixture.

"Home-Brew" Tests: see Laboratory Developed Tests.

Homozygous: term used to designate an individual with a gene which alleles are similar. In the case of TPMT, there are two homozygous profiles: $TPMT^{HH}$ and $TPMT^{LL}$.

Interferon: cell signal proteins produced by the immune system in response to viruses, parasites or tumour cells.

ß-interferon: drug used to treat some autoimmune diseases such as multiple sclerosis. Some types of ß-interferon are obtained from mammalian cells while others are produced in modified bacteria.

Laboratory Developed Tests (LDTs): Non-commercial (non-patented tests), which are done inside a research or clinical laboratory, by using commercial reagents and available protocols for using those reagents.

Large Cell Lung Carcinoma: type of NSCLC, which grows very quickly and is characterised by large and round cells.

Leucopenia: decrease in the number of white blood cells, which results in a higher risk of infection.

Lung (non-small-cell) adenocarcinoma: form of cancer that develops from the cells that line the airways, from a particular type of cell that produces mucus. It is often found in the outer parts of the lungs and is the most common type of cancer in non-smokers.

Lung squamous (non-small-cell) carcinoma: form of cancer of the carcinoma type (malignant cancer) that also develops from the cells that line the airways and is often found near the centre of the lung. This type of cancer is often due to smoking.

Mass Spectrometry (MS): analytical technique to determine the elemental composition of a substance.

Metabolites: small molecules, result of the metabolism or the biochemical reactions that occur inside an organism.

6-Mercaptopurine: anti-cancer drug used to treat acute lymphoblastic leukaemia (ALL).

Neutropenia: low number of neutrophils, the most important type of white cells.

Non-Small-Cell Lung Cancer (NSCLC): Type of cancer which accounts for 8-9 out of 10 cases of lung cancer. NSCLC can be classified in three types: squamous cell carcinoma, adenocarcinoma and large-cell carcinoma.

Off-label Drug: drug which patent has expired and is exposed to the competition of generic drugs.

Pancytopenia: reduction in the number of red, white cells and platelets.

Patent Cooperation Treaty (PCT): international law treaty which provides unified procedure to fill in patents. The first step of the procedure consists in filing an international (patent)

application with a suitable patent office, called a Receiving Office (RO). This application is usually called an international application or simply a PCT application

Phenotype: morphological characteristics of an individual, which include morphology, physical and chemical properties.

Phenotyping: measuring the morphological characteristics of an individual. In the case of TPMT, it refers to the measurements of the levels of TPMT in the blood.

Polymorphisms: type of DNA variation (or mutation) that is common among the population[1]. Strictly speaking mutations are random and polymorphisms follow a pattern, although often both terms are used interchangeably.

Radiohistochemistry: methods used to study the composition of tissues through radioactive labelling and detection.

Randomised Controlled Trial: clinical trial used to test the efficacy and effectiveness of health care services.

Single Nucleotide Polymorphism (SNP): type of polymorphism that only occurs in one of the bases (or building blocks) of the DNA.

TAX32 trial: clinical trial that investigates the efficacy and effectiveness of docetaxel, versus best supportive care as second-line treatment in NSCLC.

Therapeutic index: ratio between the toxic dose and the therapeutic dose of a drug. The therapeutic index is used as the relative safety of a drug.

Thiopurines: drugs that inhibit the metabolism of purine components, which are some of the building blocks of the DNA.

Thiopurine Methyl Transferase (TPMT): enzyme involved in the metabolism of pharmacological agents denominated thiopurines.

Tumour Necrosis Factor (TNF-α): is a chemical substance from the group of the cytokines (see definition) that triggers the programmed cell death (or apoptosis). TNF-α is usually overproduced in chronic inflammatory/autoimmune diseases, such as rheumatoid arthritis and

[1] In the text we will be using the term mutation and polymorphism interchangeably.

multiple sclerosis. The drugs that target TNF-α are denominated anti- TNF-α. These drugs belong to the family of drugs called biological agents.

Tyrosine-kinase (TK): enzyme involved in the transduction of signals inside the cell, by the transfer of a phosphate group into another protein (phosphorilation). TKs are often present in cell receptors, which trigger a cascade of reactions inside the cell.

Chapter 1. Introduction

1.1 Pharmacogenetics in the pharmaceutical context

The history of the pharmaceutical industry can be summarised in three periods (Henderson et al., 1999). From 1850 to 1945, new drug developments occurred with a research based on relatively primitive methods. The following period, from 1945 to the 1990s was marked by the large-scale development of penicillin and the need for antibiotics during World War II and thereafter. This period was characterised by the institution of in-house R&D programs and relatively rapid rates of new drug introduction, with an industry transition to R&D intensive business. At the beginning of the seventies the industry began to benefit more directly from the funding for health related research that followed the war, which led to enormous progress in the understanding of the mechanisms of the action of existing drugs and of the causes of disease. The last period, which dates from 1990s onwards, has been characterised by the mapping of the human genome and the use of tools of genetic engineering in the production and discovery of new drugs.

The integration of genetic tools into the search for cures to disease has created two trajectories. The first one dominated by the use of biotechnology as a tool for the production of proteins whose properties were already well understood; the second one, the use of biotechnology to search for new therapies. Both are now being combined.

The use of molecular biology as a production technique has led to the transformation of the existing industrial dynamics, with the creation of specialised biotechnology firms and the establishment of new collaborations between biotechnology and pharmaceutical companies. The exploitation of new knowledge and the consequences of a new industrial dynamics has resulted in the development of new tools and devices that are starting to change the drug development processes and related health services. The exploitation of some of the molecular biology tools resulted in the production of new knowledge about our human genome.

When the Human Genome Initiative was launched in 1990 it intended, not only to identify the human genes, but also to store that information in databases, transfer some technologies into

the private sector and address the ethical, legal and social issues that emerged from these procedures. From 1990 until 2003 when the final sequence was published, these and other issues attracted the interest of experts and non-experts in the field. A number of publications in areas related to genetics and health care appeared, partly driven by scientists and opinion leaders from an emergent biotechnology industry (Venter et al., 2001, Collins and McKusick, 2001, Lindpaintner, 2003, Lindpaintner, 2002) and a decaying pharmaceutical industry that was experiencing higher costs of drug development (Di Masi et al., 2003b) and a decrease in the number of new chemical entities reaching the market (Skyes, 2000, Di Masi et al., 2003b, Di Masi, 2002). These facts pushed pharmaceutical companies to search for new strategies and to envisage alternative options associated with the use of genetics and molecular biology, which, together with a combination of higher technological throughput and human skills, could revolutionise pharmaceutical R&D (Anderson, 1999, Evans and Johnson, 2001).

However, although the use of molecular genetics has had important implications for R&D processes (especially in the selection of patients that enter clinical trials), its benefits have not yet been fully translated into the delivery of new drugs, whose response could be pre-determined through the use of genetic testing (Piazzoli and Recchia, 2004). One of the reasons for this might be attributed to the fact that drug response has often a genetic as well as an environmental component and, it is difficult to prove that the response to drugs is due exclusively to genetic factors reproducible across the population. And, even where such association can be proved, its translation into the clinic is not easy.

One of the main drivers for technology adoption in a clinical setting is clinical utility. This term, although it lacks an agreed formal definition or conceptualization, is an increasingly used concept in health care, which accounts for practitioners' perspectives about the usefulness, benefits, and drawbacks of an innovation for their working practice (Smart, 2006). This concept will be used in several occasions along this thesis.

Clinical utility is an important factor in the adoption of new medical technologies in clinical practice; however, it is not exclusive. Budgets, cost-effectiveness studies, clinical guidelines or the opinion of consolidated clinical networks are also factors that affect the uptake and diffusion of medical innovations. Also the diffusion of service-based innovations, requires changes in the structure of the health care system (Greenhalgh, 2001) and these changes are more difficult to achieve when they are highly disruptive of the socio-economic, educational or professional environment, as it is the case of radical innovations.

Pharmacogenetics (PGx) and Personalised Medicine[2] is the study of the genetic variability of groups of individuals towards drug response. This discipline, which emerged from the knowledge of the human genome promised to develop better drugs and deliver more targeted services according, not to the signs and symptoms of the disease but to the genetic factors associated with it. Following the principles of PGx, if patients were to receive treatment according to their genetic profile, they would need to undergo some sort of testing that would determine the state of a disease and/or the likelihood to respond to a drug. Then, the patient would be treated accordingly.

PGx has often been associated with the term "personalised medicine", a more self-explanatory version which has, however, a different meaning. While PGx refers to the genetic factors associated to drug response, personalised medicine not only refers to the genetic but also to the phenotypic factors[3]. The two concepts will be differentiated in this thesis.

This new approach, which promises to offer more personalised therapies based on the genetic and/or phenotypic characteristics of drug response, challenges the existing norms and practices that rule traditional medicine, namely, Evidence-Based-Medicine (EBM).

EBM means integrating individual clinical expertise with the best available external clinical evidence from systematic research, understanding by individual clinical expertise the proficiency and judgment that individual clinicians acquire through clinical experience and clinical practice. EBM, therefore, looks for clinical evidence in the published literature and in clinical trials that prove the safety and efficacy of drugs. This has been defined as the *conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients*. (Sackett et al., 1996). However, the EBM approach faces a series of weaknesses, because, even after market approval, some drugs get rejected due to a lack of efficacy, which leave patients susceptible to not responding to a drug or to developing adverse reactions (ADRs). As a result, the option for patients who develop ADRs is the withdrawal of the treatment and the start of a new one, although without guarantee that the new one would give good results (this has been described as prescription of drugs on a trial-an-error basis). In this respect, personalised

2 Sometimes in the literature, the terms PGx and personalised medicine are used interchangeably; however, both terms are well differentiated in this thesis. PGx is the association between genes, genetic testing and drug response. Personalised medicine has a wider meaning and involves any (genetic and non-genetic) testing that predicts drug response. So, while one of the case studies that is going to be part of this thesis (Tarceva®/EGFR testing) involves genetic testing, the other case, (azathioprine/TPMT testing) involves both genetic and phenotypic testing.

[3] Phenotype in this thesis will refer to levels of enzyme measured in the blood.

medicine has important implications for the production of safer and more effective drugs (Robertson, 2002, Webster et al., 2004).

PGx has the potential to look for molecular targets and direct new drugs towards these and improve the drugs in the market. However, the lack of knowledge about genetics among prescribers (Hedgecoe, 2004); the lack of large prospective studies showing improvement of drug efficacy (Ingelman-Sundberg, 2004); the ethical issues that the manipulation of genetic information raises, together with the lack of consistent policy measures (Melzer, 2003, Royal Society, 2005) are major causes for its non-adoption in the clinic.

1.2 Hypothesis

This thesis will lie in the study of PGx as an innovation and how it can affect drug development and service delivery. PGx can, in principle, lead to safer and more effective drugs, by improving the drug development processes as well as the drug delivery mechanisms, which may imply important organisational changes. However, the diffusion of innovations in such a complex environment is socially constructed and continuously negotiated between the members of the organisation (Greenhalgh, 2005). Pharmaceutical companies might develop new and more innovative products, provided they foresee enough market-return, but, once these are in the market clinical implementation may not be immediate or may not reach the expected returns. Clinicians may also implement a particular medical innovation provided they believe it complies with the criteria of clinical utility, although clinical opinion may face the disapproval of some other institutional or patient organisations and this may affect how treatments are delivered.

Taking this into consideration, this thesis aims to give answer to three hypotheses:

- PGx is a radical innovation because, its translation into clinical practice requires an organisational re-structure which starts from the need to search for new drug models and is followed by the adoption of new technologies, the acquisition of new skills and guidelines, the set up of new services and, in general, a major mobilisation of resources that leads to new forms of health care delivery.
- PGx represents a paradigm shift as it does not fully comply with the norms and practices of Evidence Based Medicine (EBM), mainly because EBM has failed to explain why some drugs fail after market approval, and why ADRs are still a burden for health care. PGx however suggests that failed use of drugs is due to a lack of understanding of the molecular roots underpinning drug response, which explains why the evidence obtained

during clinical trials has not yet been able to fully explain drug response, because new drugs still cause a series of ADRs. What PGx proposes is that there is a need to apply diagnostic testing (either through genomic or phenotypic technologies), in order to accurately identify drug targets and their genetic variants. This will enable a better comprehension of the origins of ADRs and how they can be prevented.

- The use of PGx in the clinic is not systematic and does not respond to strict patterns and rules. According to the existing literature, PGx applies on a single case basis (Hedgecoe, 2004, Pirmohamed and Lewis, 2004) because the social, technological, economic and political issues that emerge in every case are different. For this reason, we would explore a series of contingent factors that may underpin PGx innovation: clinical evidence, regulatory guidelines, private interest, and patient or clinical opinion. This may explain why PGx has different levels of adoption across clinical areas and across countries.

1.3 Aims of the Research and Research Questions

Research on health service organisations has often been restricted to a single level of analysis, the individual, team or organisation, but has failed to address important interactions between different variables and levels, and has frequently not taken into account the contextual and contingent issues that influence the diffusion of technology (Greenhalgh, 2005).

The problem of how the diffusion of technology occurs and who intervenes in its diffusion is going to be tackled through the analysis of the rationales that the different actors involved in the process of diffusion hold, in order to suggest how the role of testing may change future mechanisms of service delivery. Testing is therefore the central focus of this thesis, because it will enable a shift from prescribing drugs based on a "trial-and-error" basis to prescribing drugs according to genetic and/or phenotypic profiles. So, testing is the necessary condition for PGx and personalised medicine to occur.

1.4 Research Questions

The main research questions that this research intends to answer are:

1. What are the main enablers and barriers that facilitate and/or hamper the use of PGx in the case of azathioprine/TPMT and Iressa® and Tarceva®/EGFR in clinical practice?

This question aims to understand the reasons why PGx is promising as well as controversial and why TPMT and EGFR testing are not widely used in clinical practice, although they are both promising technologies. The question aims to explore the main conflicting issues that hamper the use of PGx, and how these conflicting issues impinge on the adoption of PGx.

2. How are these enablers and barriers shaping the process of technology diffusion for TPMT and EGFR testing?

This question intends to follow the arguments that the different actors involved in TPMT and EGFR testing have in favour of or against PGx testing; how these actors position themselves in relation to the rest of the PGx world; and how they shape technological options for the use of TPMT and EGFR testing in health service delivery.

3. How may the existing controversies around TPMT and EGFR testing be generalised to a higher level of policy analysis that informs policy decisions on how PGx service delivery might be implemented in a public health care system such as the NHS?

During the exploration of the use of TPMT and EGFR testing, it is expected that there will be common emerging issues across all PGx applications, in particular in the areas of drug and test regulations, clinical guidelines and ethical frameworks. This final question intends to address, from what has emerged from each case study, common issues that have emerged from the two previous questions and suggest some general implications that current controversies may have at a policy level.

1.5 Research agenda

Due to the nature of the research on health service organisations and associated service delivery mechanisms, the research involves the compilation of different opinions and points of view of

the main actors involved in drug development and service delivery, which will serve to understand the processes of PGx development and delivery. In order to do this, we scheduled a series of semi-structured interviews with five sets of actors: researchers, clinicians, policy makers and regulators, pharmaceutical and biotechnology companies and patient groups. Specific research protocols were designed for each of the groups.

The interview data was later on complemented with document analysis that served to build the individual case studies around TPMT and EGFR testing and the following discussion on the hurdles that PGx development and delivery faces.

1.6 Overview of the thesis

The body of this thesis is structured in nine chapters. Following the introduction, chapter 2 will be dedicated to a literature review on innovation studies, followed by chapter 3 which is a review of the existing literature on pharmacogenetics and personalised medicine, with a particular focus on pharmacogenetics as a radical innovation. Following, chapter 4 will form the methodology of the thesis and the conceptual framework.

Chapters 5, 6 and 7 will represent the empirical part of the study and illustrate both case studies on TPMT testing in Spain and the UK and EGFR testing in the UK, representing current clinical practice and, in general, arguments for and against its use. Chapters 5 and 6 add another dimension to the study by comparing the level of adoption of TPMT testing in two countries and therefore, two different institutional settings (the UK and Spain).

Chapter 8 will form a discussion around how PGX affects drug development and service delivery and, finally, chapter 9 will present the common ground among TPMT and EGFR testing as well as some policy recommendations for implementing PGx in a public health system like the NHS.

1.7 Contribution to Knowledge

Since PGx raises a series of unresolved technological, economic, ethical and regulatory issues. The core of this research focused on the analysis of how these would contribute to the different arguments for and against the use of PGx in clinical practice. This analysis set the basis to inform policy on ways of improving the use of PGx in public health systems in the UK and Spain.

In order to proceed with the analysis, we gathered different views and arguments for and against the use of PGx in the clinic, through interviews with experts (researchers,

pharmaceutical and biotechnology companies, drug regulatory agencies, health regulators, clinicians, laboratories and patient associations), who provided opinions about the benefits/drawbacks of PGx in general and TPMT and EGFR testing in particular (Section 1.9 introduces the cases and highlight the main differences and similarities among them.

The major contribution of this research lies in the following:

- The systemic approach adopted during the framing of the research, which enabled a deep analysis of all the factors that underpin the STEEPV acronym and influence PGx adoption (for further information on the STEEPV, see section 2.5 and annex 7). This in-depth analysis looked both at issues at a high policy level as well as issues at the level of implementation, uncovering mechanisms through which policy implements practice and the other way around.
- The two case studies illustrate two different technological trajectories (PGx for avoiding ADRs and PGx for preventing drug response), bringing out differences in the patterns of innovation for off-patent drugs and for drugs under development.
- The comparison between TPMT testing in the UK and Spain, explains how, differences in institutional contexts affect health service innovation and access to testing.

1.8 Two cases: TwoTechnological Trajectories

Two technological trajectories have defined the use of PGx and personalised medicine (see figure 1.1). The first one refers to the avoidance of adverse drug reactions (ADRs) and the second one to the improvement of drug therapies (Hedgecoe and Martin, 2003). The cases of TPMT and EGFR testing aim to illustrate each of these technological trajectories.

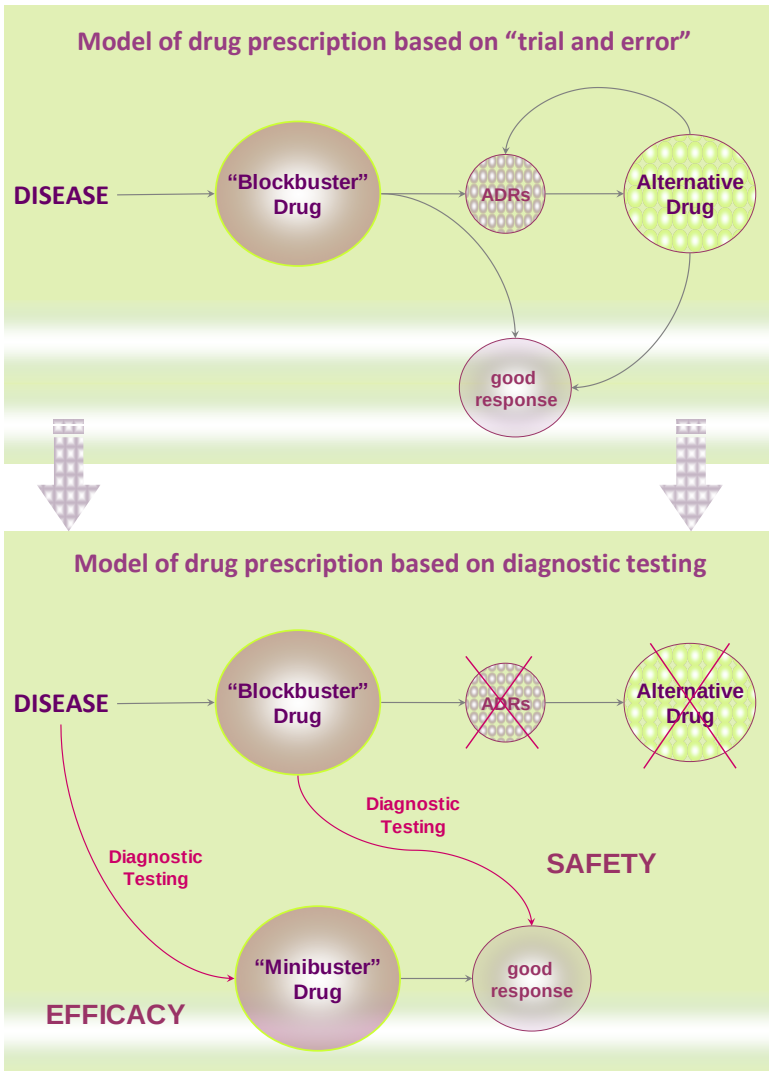

Figure 1.1- Shift from the current model of drug prescription based on trial-and-error into a personalised approach where diagnostic testing can improve the safety and efficacy of drugs.

1.9 EGFR and TPMT Testing

It is difficult to make generalisations in PGx as it is a discipline that applies on a single case basis; this research is going to focus on two specific case studies. The first one is the test that detects inter-individual differences in the enzyme, as well as the gene that codifies for the enzyme,

Thiopurine Methyl Transferase (TPMT). Mutations on TPMT were one of the first PGx biomarkers discovered. The second is the test to detect mutations in the gene that codifies for the Epidermal Growth Factor Receptor (EGFR), a test in which a relationship between lung cancer and drug response has been found recently. Both tests are different for various reasons:

1.9.1 Scope of the Test

TPMT is aimed at preventing some adverse drug reactions originated by a drug, now off-patent, prescribed in a number of autoimmune conditions, while EGFR testing looks for patients who experience a good response to new treatments for lung cancer.

1.9.2 Diseases Covered by the Test

TPMT is used by patients who are taking 6-mercaptopurine (a drug for treating acute lymphoblastic leukaemia), or azathioprine, a drug initially prescribed to transplant patients and widened later on to the treatment of autoimmune conditions, mainly in dermatology, rheumatology and gastroenterology. EGFR can potentially be used as a PGx test, as at the moment it is only used for research on patients with a particular type of cancer (non-small cell lung cancer), in order to assess whether they will respond to the new therapeutic drugs, Iressa® and Tarceva®, although at the moment only Tarceva® is approved in the UK and Europe.

1.9.3 Drugs Associated with the Test

The drugs associated with the use of TPMT testing are azathioprine and 6-mercaptopurine. The drugs linked to non-small cell lung cancer and EGFR testing are Iressa® and Tarceva®, both innovative treatments that promise better results than previous drug regimes (chemotherapy and docetaxel) and which add another dimension to the treatments of these patients; they are oral drugs and so their treatment does not require hospitalisation. However, the full safety and efficacy of these drugs is not proven yet and so only Tarceva® is approved in Europe for a restricted number of cases. One of the promises of PGx is that EGFR testing might help select the population who would respond to Iressa® and Tarceva® on the basis of EGFR results.

1.9.4 Target Population

Although the incidence of autoimmune conditions is growing, the incidence of diseases like inflammatory bowel disease (IBD), rheumatoid arthritis (RA), lupus erythematosus (LE), immunobullous diseases, eczematous disorders or photodermatoses is small (many if them are

rare diseases that affect less than 1 per 2000 people) and therefore, the population susceptible to TPMT testing in these cases, as well as in acute lymphoblastic leukaemia, is lower than the population affected by lung cancer and susceptible to EGFR testing.

1.9.5 Treatment of the Diseases

Once autoimmune diseases appear they remain chronic and patients have to follow treatments for life. Lung cancer, on the contrary, is a fatal disease and once it is diagnosed, patients follow chemotherapy regimes for a limited period of time.

1.9.6 Origins of the Disease and Patient Support

Autoimmune diseases have an unknown origin. Because they are so uncertain and these conditions last for life, patients build interest groups to seek advice and support and collect funds for further research. The number of patients that suffer from lung cancer is very large; it has one of the highest rates of mortality among cancers and has a low period of survival so patients do not tend to establish such strong networks. In addition, lung cancer has an important behavioural component (smoking) and this adds an element of blame that might hamper the establishment of stronger patient networks.

1.9.7 Institutional Environment

The case of TPMT testing will include a comparison between the UK and Spain, in order to understand the influence of different institutional frameworks on the adoption of PGx. On the one hand, the comparison aims to understand the differences in the level of support for publicly funded health research. On the other, it will look at the differences in structure and organisational arrangements of health service delivery between the two countries.

The case of EGFR testing only focuses on the UK, where no socio-economic study has been done to the best knowledge of the author.

1.10 Summary

This thesis focuses on the study of pharmacogenetics, adopting a diffusion of innovations perspective, which addresses specific issues that arise at the point of drug development and at the point of service delivery and hamper the process of diffusion into the clinic.

The thesis sets off by establishing a series of hypothesis that start by assuming that the diffusion of innovations in healthcare organisations requires important organisational changes that lead to new forms of service delivery; to follow by saying that PGx continue with a new way of understanding clinical practice as a result of the introduction of new forms of diagnostic testing in clinical practice. The final hypothesis assumes that, although PGx implies organisational changes and the new forms of understanding clinical practice and practicing medicine, PGx does not respond to strict patterns of diffusion, because the mechanisms in which group of individuals respond to a drug are different and these are also subject to other unpredictable external factors (i.e. business practices, evaluation procedures) that affect each drug differently and this influences how the technology is introduced in a clinical setting.

In terms of analysis, the thesis considers that there are a series of unresolved issues at a technological, economic, regulatory and ethical level, which originate contrasting arguments for and against the use of PGx in the clinic. These issues are studied using the STEEPV acronym (social, technological, economic, ecologic or regulatory and political), which will provide a systemic view of how different socio-technical factors underpin the use of PGx. The use of the notion of socio-technical systems aims to contribute to the existing literature on medical innovation, which has often focused on a single unit of analysis but not on the whole system. In this case, the socio-technical system is pharmacogenetics and its use in clinical practice.

Finally, the thesis aims to illustrate two case studies, TPMT and EGFR testing. The first one aims to exemplify a case of PGx for off-patent drugs and, the second, a case of PGx for pharmaceuticals under development. In the TPMT case we also included a country comparison which intended to assess differences in institutional settings and technology adoption.

Chapter 2. Literature Review

2.1 Systems and Systems of Innovation

Technology-related analysis has traditionally focused on inputs (such as research expenditures) and outputs (such as patents). However, the interactions among the actors involved in technology development are as important as investments in research and development, since they are key elements to translate inputs into outputs. Systemic approaches emerged as a tool that would give a new insight into innovative and economic performance in many countries. Since innovation and technology development were the result of a complex set of relationships among actors in the system, which included enterprises, universities and government research institutes, developing an adequate framework would help policy-makers understand these relationships and identify leverage points for enhancing innovative performance and competitiveness (OECD, 1997).

The concept of "systems of innovation" emerged in innovation studies as a promising strand of study, in which the scope of analysis broadened, from artefacts to systems and from individual organisations to networks of organisations, resulting from an increasing attention to the economic role of knowledge. The main focus on the systems of innovations approach is the functioning of the system (e.g. the comparative analysis of innovative performance of countries).

A national system of innovation has been defined as:

> *"the network of institutions in the public and private sectors, whose activities and interactions initiate, import, modify and diffuse new technologies." (Freeman, 1987)*

Systems of innovation have not only been defined at a national (Lundvall, 1992), but at a regional (Cooke, 2001) and sectoral (Malerba, 2002) level.

The definition of system includes both the supply side (innovations) and the demand side (user environment). The existing systems of innovation approach focuses mainly on the production

side where innovations emerge; however, in order to widen this analytic focus, Geels (2004) proposes another approach: he proposes to look at socio-technical systems.

2.2 Socio-Technical Systems

Until recently, the technical and the construction of the so-called technical systems was a domain for engineers, technologists or scientists. However, studies of the development of some technical objects like the bicycle or the bakelite (Bijker, 1987, Bijker, 1995), demonstrate that the social and the technical are shaped together.

Scientific facts on their own, show different stages of completion and acquire many different shapes that are difficult to understand by non-scientists. However, when these scientific facts are brought back into their "factories", namely their research laboratories and research institutes, and integrated into a particular social context, they provide an enormous amount of information about their potential use and their users as well as the enablers and barriers that facilitate or hamper their diffusion. Therefore, the diffusion and adoption of an innovation takes place in the hands of people and requires a co-evolution and a co-shaping of the technical as well as the social (Bijker and Law, 1992).

The inclusion of technology into more general accounts, requires that the technological, the economic, the political, the social and the natural, are seen as interrelated (Law, 1986). This is particularly relevant in questions about "science" that cannot be answered by "science" (Weinberg, 1972).

The exploitation of new knowledge-intensive technologies is a long and contested process that would never occur if it did not represent an opportunity for industry and markets (Gibbons et al., 1994). On the one hand, industry seeks competitive advantage through the exploitation of new inventions (innovations when they are commercially available); on the other, new inventions and innovations are highly unstable because, when they reach the market they face numerous technical, cultural, economic, ethical and regulatory constraints (Brown et al., 2000). For this reason, the initial uses that innovators anticipate for particular inventions are often frustrated because, in order to be adopted, they need to be adapted and re-shaped in order to fit within the social-economic environment where they are embedded.

Some authors explain the process of socio-technical evolution as a co-shaping mechanism in which network actors use discourses of hope and fear to enhance particular technological

expectations and deplete others (Powell and Grodal, 2005). Some sociologists of science explain the diffusion of technologies in terms of socio-technical networks formed by human and non-human actors, who hold conflicting positions and align them in an effort to stabilise an emerging network (Callon, 1987). This alignment of conflicting interests requires a process of negotiation and compromise during which some technological trajectories are accepted and others withdrawn (Dosi, 1982). So, the introduction of an innovation often occurs when a new group of actors within an emerging network starts favoring particular trajectories and begin to shape the direction of the technology towards those trajectories (Bijker, 1995), generating strong path-dependencies that marginalize competing technologies (Brown et al., 2000).

Consequently, technological innovation cannot be understood without framing it in the particular socio-economic context in which it emerges, it is used and it dies. The concepts of technological and socio-technical systems will contribute to this framing.

A "technological system" is defined as:

> *…networks of agents interacting in a specific technology area under a particular institutional infrastructure to generate diffuse and utilize technology. Technological systems are defined in terms of knowledge or competence flows rather than flows of ordinary goods and services. They consist of dynamic knowledge and competence networks (Carlsson and Stankiewicz, 1991) p. 111*

This concept set the grounds for what Hughes (1989) defined as a Large Technological Systems (LTS) approach, which refers to a particular kind of technology involving infrastructures, e.g. electricity networks or telephone systems. Technological systems contain messy, complex, problem-solving components. Among the components of LTS there are physical artefacts such as turbogenerators, transformers and transmission lines in electric light and power systems, but also organisations such as manufacturing firms, as well as other components labeled scientific, such as books, articles and university teaching and research programmes, together with legislative artefacts such as regulatory laws. The large technological system approach has a particular mode of analysis that consist in looking at socio-technical systems (ST) (Hughes, 1987).

Socio-technical systems therefore are multi-dimensional (Geels, 2008). For this reason, a number of insights from different disciplines are necessary to understand them:

- Economics and management studies focus on firms, entrepreneurs, competition between new and old technologies, competition between firms, resources, adaptation

through R&D, performance developments, industry structures and industrial networks. Often, industrial dynamics is conceptualised as market adoption (diffusion), although what users do with new technologies, how they integrate them in user practices and how they change their behaviour or preferences, is also important.

- Sociology (especially science and technology studies) focus on elements such as: relevant social groups, interpretations and views, social networks, negotiation and alignment. Analysing co-construction of technology and society, sociologists look at user contexts (user groups, their interpretations, interests, struggles).
- Political science focuses on elements such as: conflicting interests, power struggles, laws, regulations, institutional frameworks, lobbying, advocacy coalitions. Regulations and institutional alignment influence the societal embedding of new technologies. Policies are not seen as exogenous aspects that policy makers can influence at will. Policy makers are influenced by their constituencies, support in Parliament, public opinions, lobbying groups, etc.

A socio-technical systems perspective allows us to understand technology development and use in terms of the complex adaptative processes constituting the interdependencies between the material and the social (Smith and Stirling, 2008). Socio-technical systems consist of artefacts, knowledge, capital, and labor, cultural meaning, etc (see figure 2.1). The functioning of socio-technical systems results as the outcome of the activities of human actors embedded in social groups that share certain characteristics, perceptions, problem-agendas, norms, preferences etc. Each of these groups interacts with the rest, forming networks and mutual dependencies that align the activities of each of the groups together. Therefore, this socio-technical approach focuses on multiple actors and social groups, not only firms or markets but also communities or organisational fields. The virtue of this unit of analysis is that *"it directs our attention not simply to competing firms or to networks of organizations that interact, but to the totality of relevant actors"* (Geels, 2008).

Socio-technical systems focus, not only on innovations but on functionality, encompassing the production, diffusion and use of the technology. So, although firms and industries are important actors of these systems, other groups (users, societal groups, public authorities, research institutes) are also relevant.

As we can infer from figure 2.1, an artefact (either physical or non-physical) functioning as a component in a system, interacts with other artefacts, all of which contribute directly or through other components to the common system goal in such manner that, if a component is removed from a system or if its characteristics change, the other artefacts in the system will alter characteristics accordingly. As Thomas Hughes points out, "*manufacturing firms, research laboratories, university departments and other organisations are fully integrated components into a system in which physical artefacts are also components*" (Hughes, 1986).

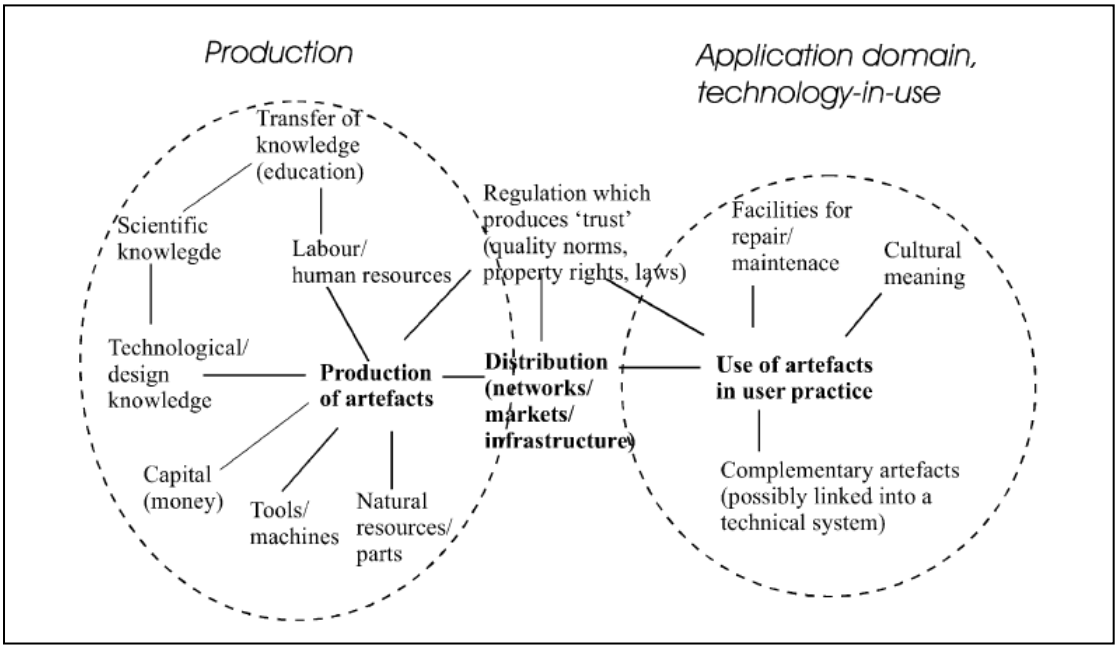

Figure 2.1: The elements of a socio-technical system. Source: Geels, 2004

The delivery of valued goods and services requires an alignment of heterogeneous elements (social and technical), although, beyond this, there is an external environment (the selection environment referred to in figure 2.2) in which the technology operates and where social movements and expectations can also exercise an important influence in the patterns of technology development. Thus here, the focus of the study of socio-technical systems does not just concern the artefacts, but the structure, agents and processes associated with these (Rip and Kemp, 1998) .

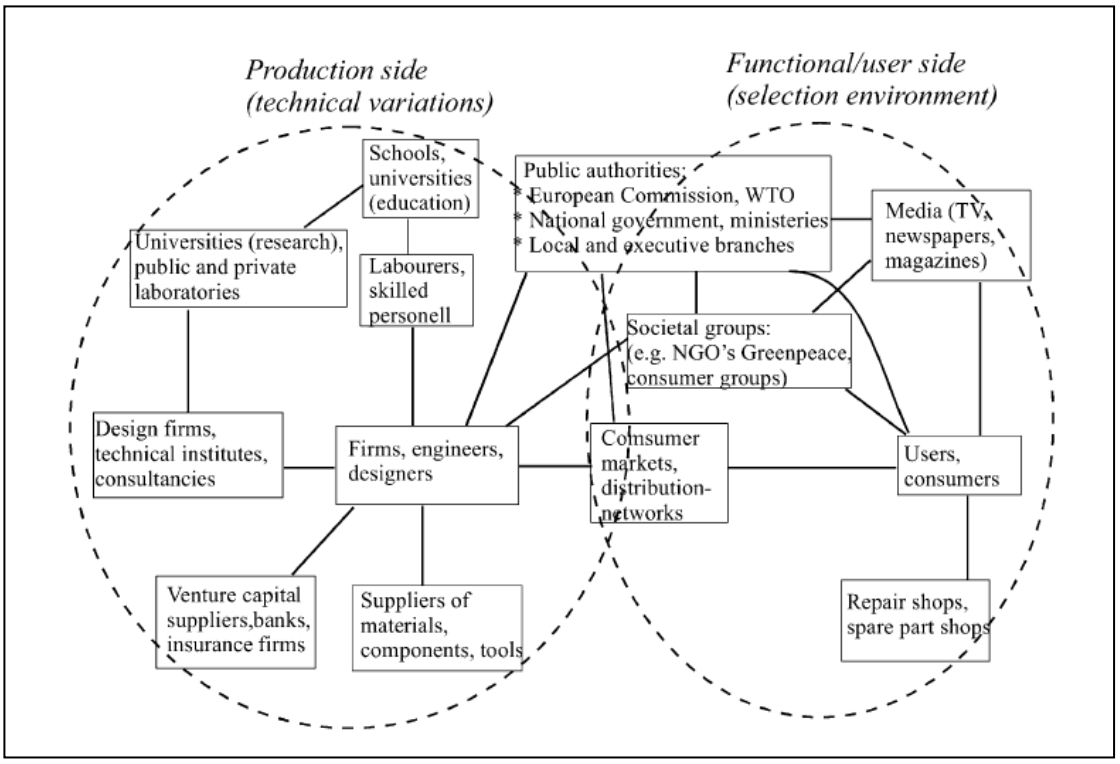

Figure 2.2: Social groups that carry and reproduce ST-systems. Source: Geels, 2004

The interactions among the elements of the system will drive its evolution. It is in the context of these interactions under which the process of diffusion of innovations will be framed.

2.3 Diffusion/Adoption of Innovations

Thomas Hughes represented the history of evolving socio-technical systems in different phases (Hughes, 1989): invention, development, innovation, transfer and growth, competition and consolidation. These phases are not sequential, they overlap and backtrack. After invention, development, and innovation, there is more invention. Then, transfer may not necessarily come immediately after innovation but occur at other times in the history of a system. During the transformation of an invention into an innovation, inventors embody in their invention economic, political and social characteristics, needed for the survival of that invention in the use world. However, because the invention changes from a relatively simple idea that can function in an environment no more complex than can be constituted in the mind of the inventors, new problems arise, resulting in a continuation of the invention phase during this development period.

Therefore, innovation reveals technologically complex systems, where the invented and developed physical components turn into a complex systemic configuration consisting of manufacturing, sales and service facilities and where, the transfer of technology can occur at any time. This is rather visible in medicine, where innovation is distributed across time, space, epistemic communities and institutional domains (Metcalfe et al., 2005) and, where the rules of interaction among these are contingent and difficult to predict. Therefore, a lengthy process of pharmaceutical research and product development does not always assure either the approval of new drugs, or the uptake of existing drugs. These unpredictable interactions explain, at least in part, the lengthy process of medical innovation and the subsequent process of diffusion and adoption. This is accentuated when the system is transferred to another time or to a different environment (where it needs to adapt). The concepts of transfer and adaptation are then tightly inter-linked. For instance, the variations in the approval mechanisms of drugs and diagnostic devices across countries are an indication of the different contextual environments in which medical innovations emerge and how diffusion and adoption are influenced by these differences.

2.3.1 Medical Innovation

Similarly to other innovations, medical technologies are embedded in a socio-technical context that influences how technology emerges, develops and translates into the clinic. This implies a co-evolution and a co-shaping of the technical as well as the socio-economic (Bijker and Law, 1992).This socio-technical system, formed by different interacting elements (technology; regulations; clinical guidelines; clinical need; development of new technological capabilities; acquisition of new knowledge; supply capability of the health system to deliver health services, or constraints in funding) shapes how new medical technologies are used in clinical practice. So, any new medical technology will only reach the clinic when the complex elements of its socio-technical network are such that it enables successful service delivery.

A common characteristic among medical innovations, which differentiates them from other types of innovation, is that they are highly regulated. This influences heavily the process of technology diffusion, which cannot occur in the same fashion as the diffusion of other less regulated innovations. At the same time, institutional settings within national borders are important driving forces in the innovation process.

Generalisations in the process are difficult not only because the aforementioned reasons but because innovations in the medical field are heterogeneous and vary from new products to a

wide range of associated health services. In addition, medical innovations have different natures: they can involve therapeutics (targeted at preventing or combating disease) or diagnostics (aimed at assessing susceptibility to disease or drug response). Some medical technologies are more invasive than others, some of them can involve testing the blood or testing the genes and not all raise the same regulatory and ethical concerns. Therefore, managing health care innovation at the same time as spreading good clinical practice, is a critical issue (Cunningham et al., 2005) that involves an understanding of the driving forces underpinning these innovations, as well as the socio-political environment that drives health policy and practice.

Medical innovations need, then, to fit within the complicated socio-economic environment formed by health organisations, national boundaries, institutions, regulations, communities of practitioners or patient organisations. Dealing with this complexity explains why the diffusion of innovations is not instantaneous.

Understanding the evolution of socio-technical networks in terms of invention and innovation and the associated problems with diffusion, together with the retarding factors that limit this diffusion (Dosi, 1992) lie at the core of this thesis, with a special focus on innovation and health service delivery through the UK's National Health Service (NHS) and the Spanish National Health Service (Sistema Nacional de Salud or SNS).

2.3.2 User-Producer Interactions

While evolutionary economics and business studies tend to focus on the production-side and the creation of knowledge and innovation, with less attention to the user side; innovation studies, more recently focused their attention on the co-evolution of technologies and markets (Coombs et al., 2001). These studies open the "black box" of adoption, which is not passive but requires adaptations and innovations in the user context. New technologies have to be adapted to fit in concrete routines and applications, this is particularly important in medicine.

The adoption of medical technology is neither a passive nor a unidirectional process. In order for diffusion to take place, it is not enough for innovators to place new medical inventions onto the market. The diffusion of technological innovation responds to a series of interactions and feedback mechanisms between the users and the developers of a technology and with the demand, and supply forces determining these feedback processes (Gelijns and Rosenberg, 1994). The fact that interactions among users and producers of technology drive the process of

diffusion, contradicts the idea disseminated by Rogers that diffusion is a linear process. Rogers, who defines diffusion of innovations as *the process by which an innovation is communicated through certain channels over time among the members of a social system* (Rogers, 1962 pp. 5) assumes that a new technology replaces an old one without changes through the innovation process, taking for granted that, in the case of medical technologies, once the uncertainty associated with the R&D processes is overcome, the translation into clinical practice is a direct process. However, while there is an inherent uncertainty associated with medical R&D, much uncertainty associated with a new technology can be resolved only after extensive use in practice, because actual adoption constitutes only the beginning of an often prolonged process in which important redesigning takes place (e.g. a drug withdrawn from the market, a new drug indication).

Von Hippel proposed that innovation processes are distributed across users, manufacturers, suppliers and others, highlighting the importance of shifting from manufacturers-as-innovators into user-producer interactions as a source of innovation (Von Hippel, 1988).

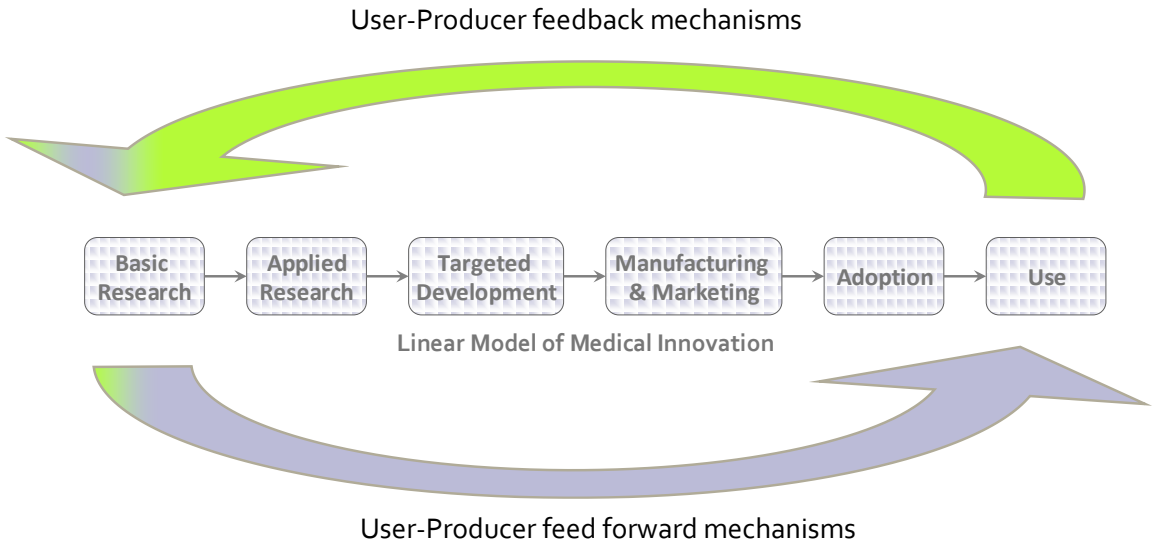

Figure 2.3 : Illustration of the linear model of medical innovation challenged by a series of user-producer feedback mechanisms that drive the process of technological change

In medicine, these user-producer interactions often take place among: clinicians who prescribe drugs to patients; patients who might report adverse events to clinicians; clinicians feeding in any information about unexpected drug reactions to the drug regulatory agency; the drug regulatory agency informing the manufacturers, at the same time as the manufacturer also informs the drug regulatory agency about the process of post-marketing surveillance and

suspected adverse events (see Figure 2.3). According to Von Hippel, these user-producer interactions control the survival of new technological artefacts in the market and ensure a demand for them (Von Hippel, 2005).

So, even if the widespread introduction of a new drug into clinical practice confirms a high degree of effectiveness, as has emerged from clinical trials, once the drug is distributed to the patients it might originate a series of unexpected adverse reactions, which may end up in a restriction of the initial indications of the drug or the improvement of the drug based on subsequent research. Consequently, because the first drug is often not the optimal version (drug regulatory agencies, together with the drug manufacturers have established post-marketing surveillance mechanisms), incremental improvements after adoption play an important role in pharmaceutical development (Gelijns and Rosenberg, 1994). Thus, with new medical innovations, good clinical performance proven during clinical trials is only one among various factors involved in the process of diffusion.

Economists highlight the importance of network effects and social connectedness in the process of diffusion, because the adoption of innovations requires absorbing mechanisms induced by social feedback effects or, what they refer to as network externalities (Arnold and Hall, 2005).

The role of users throughout the innovation process led to the introduction of the concept of *lead user,* which defines people or organisations leading to an emerging trend, who foresee needs that will later on be experimented with by other users ("the laggards") (Von Hippel, 2005). *Lead users* acquire an important role during the process of diffusion, because they act as early adopters of new technologies and therefore are the first ones to foresee further needs and enter into the user-producer feedback loop that will lead to subsequent improvements in the technology.

Therefore, the diffusion of PGx into clinical practice is likely to follow an S-curve, similar to other innovations (see figure 2.4), which shape depends on how the interactions among user-producers disentangle, as well as how the initiators trigger widespread use.

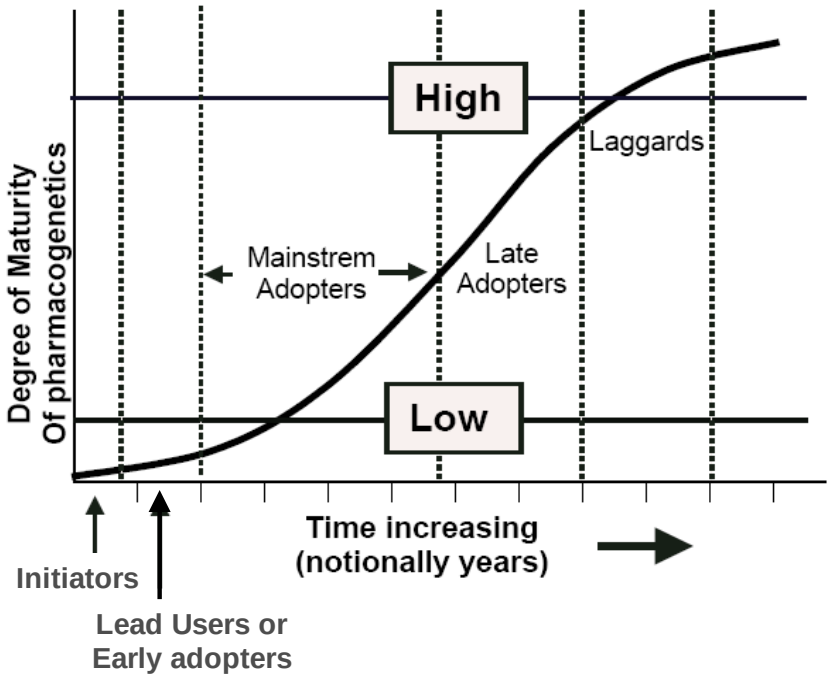

Figure 2.4: Adaptation of the S-curve of technology diffusion to PGx. Adapted from Loveridge (2008)

2.3.3 Dealing with Contingencies

The process of invention, innovation and technological diffusion in health care (or also translational research or technology transfer) brings together different actors: the drug industry, health care providers, researchers, clinicians, patients, regulators and policy makers. All are involved in the diffusion of medical technologies, although clinicians are frequently considered the final users of the technology and the locus of the demand and service delivery is strongly driven by networks of clinicians (Ramlogan R., 2006). However, often, the information asymmetry between clinicians and patients, together with the clinicians' ability to manage resources, turn them into the gatekeepers of medical innovation. Patient advocacy groups are increasingly taking a more active role in the demand for medical innovations and the associated service delivery mechanisms (Rye and Kimberly, 2007), although clinical opinion still prevails.

Medical innovation is also exposed to a broad range of unexpected events or contingencies (e.g. drug failures, adverse events, malpractice suits; that cannot be explained exclusively through medical actions) (Greenhalgh et al., 2004). When unexpected events occur, regulatory bodies, advocacy groups and the public have an important role to play in shaping the process of technological diffusion. They then mobilise different elements of the health system, to respond to these unpredictable changes. This explains why the literature argues that PGx and personalised medicine apply on a single case basis (Hedgecoe, 2004), because the drivers for

diffusion depend on contingent factors that are difficult to anticipate and have consequences that are difficult to predict.

According to Van de Ven, although some of the drivers that influence innovation might seem random and unpredictable, innovation development follows a pattern that he defines as a "non-linear dynamic system" (Van de Ven et al., 1999). This model holds that, although innovative behaviour is unpredictable, it aims to achieve desired outcomes and these bring some sort of "order" into the process of technological diffusion: the development of new ideas and the engagement of people in transactions within a changing institutional and organisational context. So, even though the whole process of innovation and technological diffusion is unpredictable, the rationales for those processes to occur respond to some planned actions, such as the necessity of solving a specific technological problem or the search for new business.

According to Van de Ven, innovation processes are based on a trial-and-error process of learning between entrepreneurs, resource controllers, and the environment, which, translated into the case of PGx, means: drug and diagnostic companies involved in the technical processes of the innovation; regulators and policy makers who assess the feasibility of using the technical artefacts (developed by entrepreneurs) in a clinical context, and patients, together with the lay public, all of whom, with different degrees of understanding and engagement with the technologies, position themselves for or against their use and exert certain levels of influence over their technological diffusion.

2.3.4 Dealing with Uncertainty

Health care has experienced important improvements in the last century due to an increase in medical knowledge and better approaches to preventing and fighting disease. These improvements have been the result of research-intensive activities and technological advances aiming to improve health and quality of life and, often, implying a shift in the established mechanisms of health service delivery. However, technical progress in medicine is slow and the introduction of new medical technologies is often contested because, when a new medical technology emerges, it is surrounded by uncertainty and risks around its clinical validity and utility and, in situations of uncertainty like these, technological visions serve to give the technology a time, a space and a particular use and, because of this we assume they are good technologies (van Lente, 1993). These visions, often based on discourses of risk and uncertainty (Brown et al., 2000), vary depending on who constructs them. There may be a difference, for example, between how a private company represents the future of a technology under

development and how a clinician, who might be resistant to the introduction of that technology because it involves changes in established clinical procedures, represents it. Similarly, these two visions will be different to those of a patient group, for whom new technologies might embody potential solutions for their clinical conditions. So, visions of the future are constructed by individual actors depending on their own personal interests and, by doing so, they enlist support and resources, construct potential technological applications, configure potential uses (van Lente, 1993) and present how medical innovations will be used in the clinic and sold in the market. Visions of the future are particularly relevant because, once they are shared they demand action and appear to be a necessity and this is often a strategy that innovators follow (Van Lente, 2000) and, as a result, these powerful narratives associated with an anticipated future impact of technology characterise "enabling" technologies around which corporations build organisational strategies and policy-makers define specific policy lock-in's (Brown et al., 2000).

Therefore, the success of new technologies depends on how developers promote their inventions in the name of "technical progress" (van Lente, 1993), stressing the good and limiting the discussion of other aspects deemed to be irrelevant (Gibbons et al., 1994). As a consequence, the broad range of technological options is narrowed down and becomes misrepresented in those visions.

Technological visions are a useful tool to address the hurdles that invention and innovation face at the early stages of development. Different visions lead to different uses of technology, although not all of them can coexist and, while some visions are accepted, others are rejected. The mechanisms that favour some visions and not others are contingent and depend on how new knowledge is produced in the context of socio-technical relations (Martin, 2001). Because new knowledge inevitably leads to a new set of interactions between the social and the technical factors, this is an indication that innovation is as technical as it is a social achievement and so technology cannot be black-boxed but needs to be inserted into a social system. Therefore, the differences between technologies lie, not in the technologies themselves, but in the contingencies and socio-economic circumstances that favour one over another (Brown et al., 2000) and these also include the expectations, uncertainties and controversies generated around new technology.

2.3.5 Challenging Traditional Diffusion of Innovations Theory

Addressing the organisational context in which medical innovations emerge implies acknowledging the fact that those innovations need to be adopted, because without adoption and diffusion, innovation would have little social or economic impact. The adoption and implementation of innovation has been traditionally explained through concepts addressed in the diffusion of innovation literature, which classical approach was developed by Rogers (Rogers, 1962). Under this model, diffusion is seen as the spread of ideas, mainly by imitation, with a special emphasis on the influence of social networks and how opinion leaders and individuals take adoption decisions. This concept stands on five principles: (1) the degree to which the innovation is perceived as being better than the previous one (relative advantage); for instance whether it represents an advantage in effectiveness and cost-effectiveness; (2) the extent to which it is perceived as being consistent with the existing values, professional norms and ways of working (compatibility); (3) the complexity of the innovation, the barriers that need to be overcome and its difficulty of being used; (4) the possibility of experimenting with the innovation (trialability) and (5) the degree to which its results are visible to the intended adopters (observability). Innovation would be more easily adopted if the potential adopters could adapt and modify (or "reinvent") the innovation to suit their own needs and innovations would be more rapidly "diffused" the more they complied with these principles.

This model later on, adapted to medical sociology to explain the introduction of tetracycline in clinical practice (Coleman et al., 1966) and to show how interpersonal communication among clinical peers influenced the diffusion process (Stocking, 1985), has been criticised for various reasons:

Clinical acceptance cannot be considered as the exclusive element of technology adoption because health care innovations are very heterogeneous and it is not easy to establish a systematic mechanism or model to which all medical technologies can adapt (Rye and Kimberly, 2007).

The diffusion of innovations does not occur by inertia, it is the result of a continuous transformation triggered by continuous interaction among people who are interested in the technology and do something with it (Callon, 1986a, Callon, 1986b, Callon, 1987, Latour, 1986).

The diffusion of medical technologies involves a variety of institutions and actors, who have different agendas and interests in the technologies. These actors and institutions, during the process of diffusion, need to align their differing interests through a process of collective social

learning that will lead to the acceptance of certain technological trajectories and the rejections of others (Dosi, 1982).

In addition, Rogers' five step unidirectional rule is not applicable to medical innovation because:

- Technological change in medicine relies on a series of feedback mechanisms among users and producers, who engage in a series of interactions that contribute to the re-shaping of the innovation (Gelijns and Rosenberg, 1994). So, even after a drug has been approved (on the basis of clinical trials that use a limited sample of individuals), pharmacovigilance mechanisms look for unexpected adverse events and side-effects that could not be identified during the clinical trials. After this information is assessed by regulatory agencies, it is taken up by the manufacturers in order to improve the drug. Therefore, the feedback mechanisms that drive technological change in medicine are highly controlled by the pharmaceutical and medical systems.
- Medical innovation is highly regulated, both at the point of development (by the FDA, MHRA, EMEA, AGEMED) and at the point of service delivery (by the rules that control the health care system in which the innovation is implemented) and regulations also contribute to these feedback mechanisms, which turn the process of diffusion into a non-linear one. National health care systems are not conventional competitive markets. They are dominated by funding constraints and different degrees of equity of access (Attridge, 2006).
- Rogers talks about consumers as the final users of the innovation. In the case of medical innovation, the definition of consumer is blurred and depends on the particularities of individual health care systems. In the UK, for example, health care is delivered through the NHS, which acts as a "filter" for access to medical innovation. Also, within the health system, clinicians integrate cost and budgetary considerations into decisions regarding the reimbursement of new medicines, acting as gatekeepers of new drugs and medical technologies, often controlling patients' capacity to choose.
- The existing institutional arrangements that control health service provision and define health policy are important characteristics of medical innovation, and will inevitably affect the process of diffusion.

2.4 Informing Policy: The STEEPV analysis

As we have seen in the previous sections of this chapter, the diffusion of medical innovations is a slow process, which is highly dependent on the compliance with strict regulations that control, not only the process of development but also the access to the market. Similarly, market access relies on a series of interactions among users and producers that continuously shape and re-shape the use of the technology and thus, the process of diffusion. But, as we have also seen previous in the chapter, this process of diffusion is also heavily contingent as it is exposed to issues that are difficult to anticipate.

New technologies are, therefore, surrounded by a situation of complexity difficult to deal with. In the case of PGx, there are still knowledge gaps and uncertainties that, we anticipate, may hamper the process of translation from development to delivery and therefore, hinder the establishment of policies that facilitate the translation into clinical practice.

The outcome of this thesis is informing policy on ways to improve the delivery of PGx treatments in a public health system such as the NHS, for this reason we needed an analytical tool that helped us identifying the existing bottlenecks that lead to the non-use of PGx in the clinic. This tool is the STEEPV acronym (Loveridge, 2004), which enables to gather information from six elements that are relevant for PGx adoption. These six elements are: sociology, technology, economy, ecology (or regulations), politics and values (or ethics).

We believed that the STEEPV analysis was particularly relevant for the purpose of this thesis since it brought together elements that align issues of PGx policy and practice. For this reason and, as it will be illustrated in the following chapters, we have dealt with each of the different issues of the STEEPV acccronym in the case studies and later on in chapters 8 and 9. We thought that these issues were relevant to improve the use of PGx in the clinic.

2.5 Setting the Research in the context of Innovation Studies

The use of the STEEPV acronym in the context of PGx aims to contribute to the existing literature in the field.

There are a number of studies that have focused on the study of pharmacogenetics. From an innovation point of view, some of these studies have analysed in what ways the use of diagnostic

testing and PGx would affect the drug development process (Nightingale and Martin, 2004) and in what forms new drugs would be delivered and what consequences these would have for the pharmaceutical and biotechnology industries (Webster et al., 2004, Lewis, 2003). Other work has looked at possible innovation strategies companies may take when adopting the use of PGx (Webster, Martin et al., 2004). Others studies have looked at how PGx has dealt with some of the problems of existing and new drugs and how this has shifted the understanding of disease and the way drugs are designed (Hedgecoe and Martin, 2003). Other studies have analysed the implications of the introduction of PGx in clinical practice for the medical profession (Hedgecoe, 2004). From a policy perspective, extensive work has been funded by the Nuffield Council of Bioethics (Melzer, 2003).

The research presented here sets out from a different angle. Taking into consideration the previous literature, this thesis aims to understand the reasons for and the influence of the differing perceptions among the industry, clinicians, regulators, policy makers and patients, which are currently leading to the non-adoption of PGx in the clinic, identifying present gaps in knowledge and the arguments that drive regulatory directions.

2.6 Summary

This chapter aims to summarise the literature on systems of innovation and socio-technical systems, which is relevant for the object of the study of this thesis: the diffusion of pharmacogenetics into clinical practice. Along the chapter it has been pointed out that technological innovation cannot be understood without framing it in the particular socio-economic context in which it emerges. For this, the literature review highlights not only the inputs and outputs that are necessary for technological development, but the process and the means by which technological development occurs, focusing in particular in the web of relationships and linkages that constitute the socio-technical system in which pharmacogenetics is embedded.

The chapter aims to give an idea of the dynamic processes that are at the core of the shaping and re-shaping of pharmacogenetic developments and clinical outputs, which involved the interaction of a series of heterogeneous elements (i.e the economic, the political, the social and the natural). However, it also points out the difficulties that technology diffusion faces in such a heterogeneous environment where different actors have often differing interests in the technology and frequently, conflicting views about its benefits.

In order to explain the points of conflict that are inherent to the diffusion of medical technologies, the chapter introduces some elements of the diffusion of innovations in healthcare. Medical innovation, in opposition to other innovations is heavily regulated to ensure safety; nevertheless, safety is often a problem even after market approval. For this reason, the improvement of a medical innovation is highly dependent on user-producer interactions, whereby user's experience provide an input for further improvement.

Chapter 3. PGx in context, from Drug Development to Service Delivery

In order to understand the series of scientific, technological, economic and socio-political challenges that PGx faces, will position the technology within a space that represents a series of relevant events that take place during pre-marketing and post-marketing of a drug. This set of events will serve to place PGx within a space where drug development and service delivery are represented, in order to understand how it challenges existing pharmaceutical business and clinical models. **The diagrams are represented along a timeline; however, this is not intended to adhere to the assumption that PGx innovation and service delivery are linear processes. The diagrams below are only intended to be used as a way of understanding PGx in the context of drug development and service delivery, which are not unidirectional but involve a series of feedback mechanisms among users and producers.**

Medical innovation is a process of social interaction among users, producers, regulators and the public that leads to incremental changes in equipment, techniques, drugs or guidelines that induce further changes which define scientific and technological trajectories (Metcalfe et al., 2005). These incremental changes, which contribute to the radical outcome in PGx, refer to scientific advances in genomics research, to the development of associated genomic technologies and their use during drug development, to the setting-up of testing facilities in hospitals, and to the inclusion of PGx and personalised medicine in routine clinical practice. These incremental changes need to be accompanied by enough clinical evidence to support the clinical utility of the new drugs, the new pharmacodiagnostic tests or other associated services; by cost-effectiveness studies that ensure that PGx and personalised medicine can adjust to existing reimbursement policies; by clinical guidelines that guarantee adequate standards of practice and by the setting up of ethical and regulatory frameworks that warrant the safety and confidentiality of PGx and personalised therapies.

Therefore, PGx and personalised medicine are likely to be disruptive because their inclusion into healthcare practice may require important changes in the way the health care organisations

operate and, unless the health service understands what the real implications of PGx are and moves towards developing the necessary mechanisms to achieve the necessary incremental steps towards establishing new ways of diagnosing disease and treating patients, PGx and personalised medicine will not reach the clinic (Nightingale and Martin, 2004).

The first of the two diagrams illustrated below (see Figure 3.1) represents the current situation of PGx, highlighting (in red) the situations that the pharmaceutical industry faces through the process of drug development and regulatory approval. The second diagram (see Figure 3.2) represents the contribution of PGx to solving or alleviating some of these situations, as well as the consequences that the implementation of PGx drugs will have for service delivery.

As is illustrated in Figure 3.1, the situation that the pharmaceutical industry faces are the following:

- Drugs fail during clinical trials because they do not achieve the expected clinical outcome.
- Drugs may not be approved by the European Medicines Agency (EMEA), or may be withdrawn from the market, because of unexpected ADRs that could not be identified during clinical trials. The EMEA reviews the safety and efficacy of new drugs every five years.
- In the UK, the Medicines and Health care products Regulatory Agency (MHRA) may restrict the use of a drug because of reported ADRs. Only rarely will drugs be withdrawn from the market by the MHRA.
- Even when a drug has been approved by the EMEA and the MHRA, its cost might not be reimbursed by the NHS because it is not cost-efficient. In those cases, the National Institute of Clinical Excellence (NICE) would not recommend the use of the drug within the National Health Service (NHS) setting.

In the light of this situation, PGx proposes a series of alternatives, as shown in the second of the diagrams (see Figure 3.2):

- The discovery of biomarkers of drug response (e.g. specific mutations on a gene) can give an indication of possible drug targets affected by those mutations; targets against which drugs could be designed.

- If there is a clear association between a biomarker and a drug, it would then be possible to pre-screen, during clinical trials, who might respond well to the drug, narrowing the population eligible to enter the trial.
- The discovery of biomarkers associated to drug response could be translated into diagnostic tests co-developed together with drugs, in which case the current model of drug development based on "blockbuster" drugs (or drugs directed to certain conditions or symptoms) would shift to "minibuster" drugs (or drugs directed to patients according to the result of the diagnostic test).
- The co-development of drug and tests would improve the safety of drugs and would prevent the number of unexpected ADRs, and withdrawals from the market because of these unexpected ADRs.
- A more targeted prescription of drugs according to the results of diagnostic tests would improve the chances of a good response and this would be an incentive for reimbursement within the NHS, in particular with very expensive drugs.
- The need to deliver diagnostic services will require specialised testing facilities within existing or new laboratories.
- Diagnostic testing will also impact on the way clinicians treat patients and the way pharmacists prescribe drugs. They would both need to have a clear understanding of what the implications of testing would have for drug prescription.

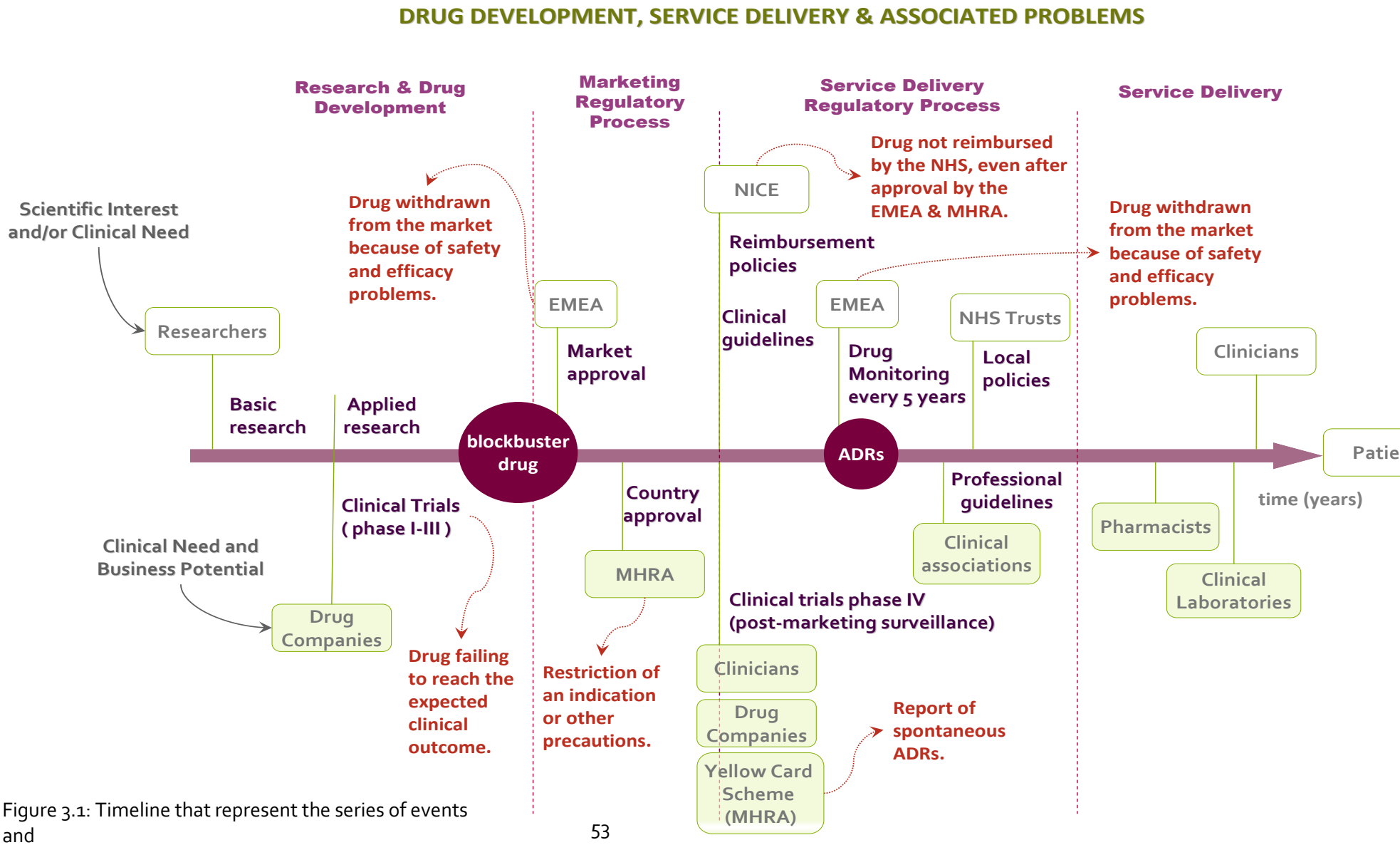

Figure 3.1: Timeline that represent the series of events and
key actors that intervene throughout the process of drug development and service delivery

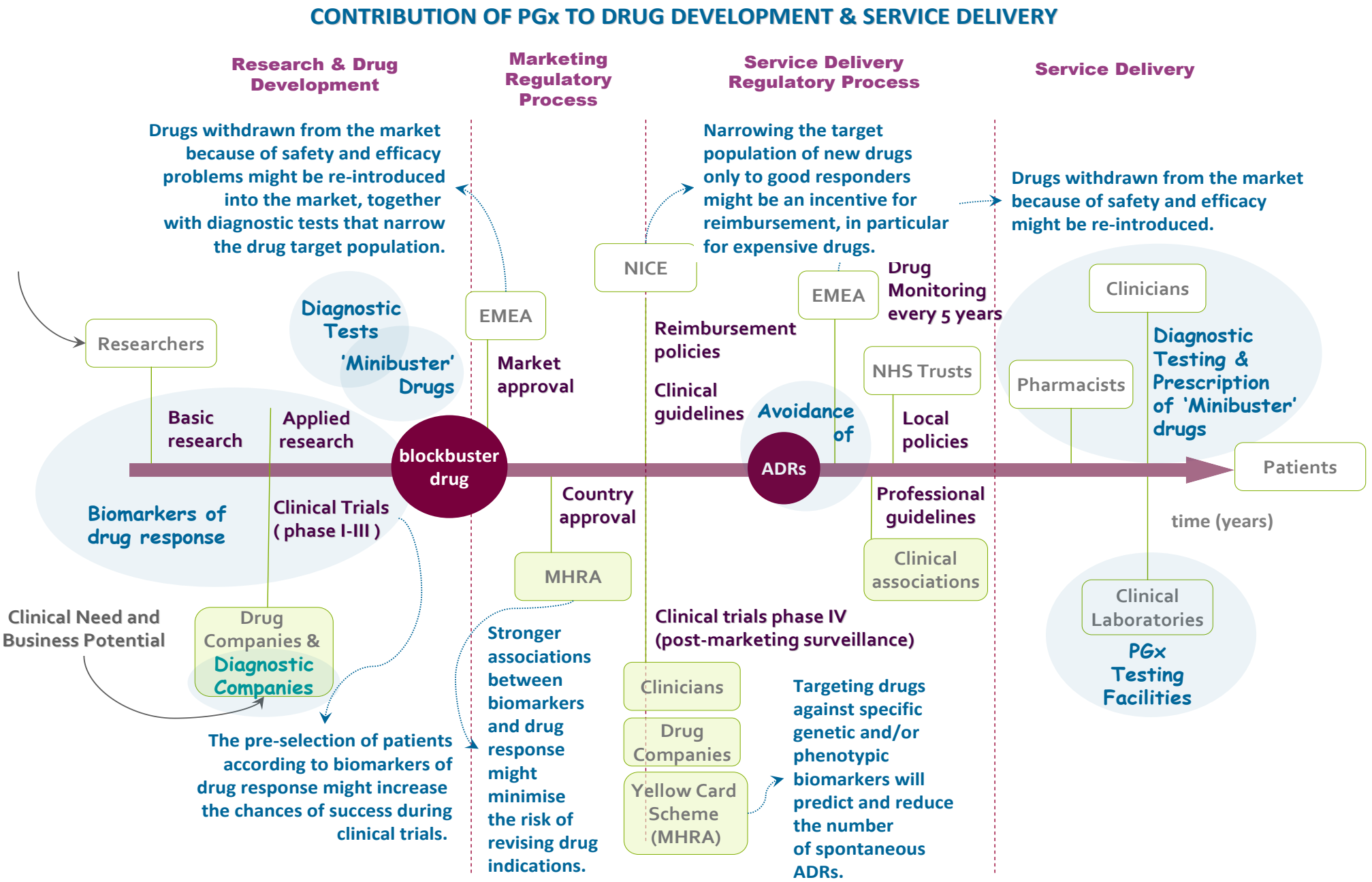

Figure 3.2: Influence of PGx on drug development and service delivery.

3.1 PGx and drug development

PGx has the potential to improve the efficacy of drugs under development and thereby contribute towards ameliorating the problems of the pharmaceutical industry. However, with the exception of cancer, the industry has not been proactive in developing PGx applications in the drug development process (Arnold and Hall, 2005) (although there is a growing interest in searching for molecular and genetic biomarkers that intervene in drug response). This may be because PGx is likely to be valuable in only a small fraction of medicines under development, and so this generates a reluctance to embark on programs that include PGx evaluations (Lindpaintner, 2003).

The engagement of regulatory agencies in PGx was not proactive until 2001, when the US Food and Drug Administration (FDA) and the European Medicines Agency (EMEA) reacted to the inconsistent evidence about the impact of PGx on drug therapy (Webster et al., 2004). They provided guidance on how and when to submit PGx data during drug development and how it could be used for decision-making (FDA, 2005). The aim of this guidance was to encourage private companies to include PGx data during drug development as well as to facilitate scientific progress in the field of PGx.

3.1.1 The "Crisis" of the Pharmaceutical Industry

The global pharmaceutical market was valued in 2006 at US $650 billion and is forecast to grow to $900 billion by 2011, with pharmaceuticals being the most important health-related products traded (55% of all health related trade), followed by small devices and equipment (19%) (Smith et al., 2009). PGx and personalised medicine emerged at a time when the pharmaceutical industry was facing a series of difficulties. The increasing number of failures during drug regulatory approval processes, problems in the characterisation of drug-dose effects and a series of difficulties in measuring the balance between the risks and benefits of new drugs were at the root of the decrease in the number of new chemical entities on the market (Di Masi et al., 2003a). Although there is a steady increase in the budget for drug research and development over the last decade, the drug industry has been suffering from a downward trend in the number of new drug marketing applications and approvals (Arnold and Hall, 2005). Between 1998 and 2002 the average annual number of new drugs approved by the FDA was 68; by 2003, this number had dropped by two-thirds. In 2004 the number of

approved drugs was 21 (Need et al., 2005). Any new medicinal compound entering Phase I clinical trials have only an estimated 8% chance of reaching the market (FDA, 2004b) and even after reaching the market, drugs can be withdrawn because of safety concerns: from 1990 to 2006, 38 drugs were withdrawn from major markets due to safety problems (Shah, 2006).

In addition to this, the increasing constraints on clinical development due to a higher burden from regulators, the need to develop more complex clinical products that required longer clinical development processes, the fact that clinical trials had to be conducted over longer periods of time to ensure effectiveness in chronic patients and special subpopulations, and the need to carry these trials out on a worldwide basis to ensure global marketing strategies and cost-effectiveness, were some of the additional barriers that new drug development processes encountered (Milne, 2002). All these elements put the pharmaceutical industry on alert to mobilise the necessary efforts to look for alternatives that could bring innovative drugs to the market (Norton, 2001).

3.1.2 The Underpinning Science

The first step towards finding personalised therapies lies in the scientific discovery of new associations between genes and/or phenotypes and drug response. Drug response is not the product of a single gene but of multiple genes and of the interactions between genes and the environment. Many of these gene-gene and gene-environment interactions are unknown and difficult to predict, turning PGx into a complicated field of study.

Biomarkers are indicators of a biological state and therefore biomarker research is the initial step towards acquiring a full understanding of the underpinning reasons for drug response. Genetic sequences can then be used as biomarkers that predict individual responses to drugs. Finding the correct biomarkers is crucial for the understanding of PGx and personalised medicine.

Advances in research into biomarkers will inevitably lead to advances in genetic sequencing technologies, as finding new genetic sequences necessarily requires sequencing technologies that decode the DNA. Inventions in this area have grown rapidly and reached favourable economies of scale. The costs and the time involved in sequencing a whole DNA have decreased considerably and, while the first sequence of the human genome took thirteen years to decipher, at a cost that came to nearly $3 billion (in 2003), six years later, sequencing

a whole genome costs $100,000 and this cost is expected to decrease to $1,000 by 2014 (Service, 2006).

New biomarkers that index the individual genetic differences in disease predisposition, progression and response to drug treatments are needed and the rapid advances of genetics are already a contribution towards this. However, the discovery of these biomarkers is not sufficient for the drug industry to develop personalised medicines. The integration of biomarker discovery into drug development programmes will need to occur at an early stage of the drug discovery process and only then will research into biomarkers research enhance the drug pipeline (Meyer and Ginsburg, 2002). Moreover, as new biomarkers are discovered, the health care system will need new approaches to understanding clinical practice and providing health services. Academia and pharmaceutical companies need to work together and establish new partnerships, because the current perception is that the industry has the money and the academic medical centres the labour force, but there is not always a concerted effort to make the most of each (Bukaveckas, 2007).

3.1.3 New Business Strategies

If the existing drug models were not enough to maintain the innovative capacity of the drug industry, then the industry had to look for alternatives that boosted their capabilities to compete in the market. Some of the strategies used in the past have been mergers with and acquisitions of smaller firms; partnerships with other research-intensive start-up firms; outsourcing of R&D functions or direct investments in new technologies (Martin and Morrison, 2006). In addition to this, if PGx promised to ameliorate some of the difficulties in drug development, then the pharmaceutical industry might consider its adoption. But investing in radical innovations such as PGx is highly risky and costly. For this reason, the drug industry has had to rely on "outsiders" (often small pharmaceutical firms or biotechnology companies), who do not have a long-established infrastructure to defend or maintain and so they have little to lose in pursuing radical innovations and are very research intensive. On the contrary, established pharmaceutical companies had abundant reasons to be slow to mobilise radical innovations because they have huge investments in current technology and often ignore radical innovations when they first appear and their survival is not very clear (Utterback, 1994).

Biotechnology companies are often small and research intensive, and often emerge from universities or research centres. They are very innovative: their developments hold a high

level of risk and uncertainty. Pharmaceutical companies, however, have the resources to be the holders of patents for blockbuster drugs. Although they have been forced to increase their efforts to include biotechnology innovations in their drug development processes, in order to overcome the crisis in the industry, it is often small biotechnology companies who first engage in complex genetic technologies and who later on seek collaborations with big pharmaceutical corporations who can support the costly clinical trials.

3.1.4 From "Blockbusters" to "Minibusters"

Traditionally, pharmaceutical companies have developed drugs targeted at specific clinical conditions and their associated symptoms. These drugs are designated as "blockbuster" drugs, because they target a broad population irrespective of the genetic or phenotypic determinants that may influence its response. "Blockbuster" drugs follow the principle of "one-size-fits-all", although it is now known that, even after a drug has reached the market, it may still be subject to safety problems and may instigate a number of adverse drug reactions (ADRs) (Pirmohamed et al., 2004, Need et al., 2005) because the development of these drugs does not take into consideration the individual genetic and/or phenotypic characteristics that determine how a drug is metabolised by each individual.

The proposition of PGx is investigating the genetic/phenotypic inter-individual variability underpinning drug response so that drugs may be targeted towards specific genetic/phenotypic sub-populations. This would require the use of genetic diagnostic testing which has implications for the existing pharmaceutical business models, which might see (if PGx is ever implemented widely) a shift from "blockbusters" to "minibuster" drugs and important changes in the drug development process (Shah, 2003). In order to do this, it is necessary for the industry to identify new drug targets, accelerate the discovery of biomarkers of safety and efficacy, include them in the drug development process, co-develop drugs and tests (Katz et al., 2002) and create standards for diagnostic testing that guide the delivery of the new "minibuster" drugs (Arnold and Hall, 2005).

At present, there is an increasing interest in developing PGx applications, and companies are exploring their benefits, especially at the early stages of drug development. At the same time, regulatory agencies are moving towards building a regulatory review process in conjunction with the drug industry and public health systems, so that the costs associated with drugs can be reduced (Danzon and Towse, 2002). However, there still need to be more prospective clinical trials that provide more PGx data (Bukaveckas, 2007).

3.2 Special factors relating to PGx: Marketing Pharmaceuticals

The marketing of pharmaceuticals and medical devices requires the acquisition of patents that protect the product from imitators. However, the marketing process for drugs and other therapeutics is different from the marketing process of pharmacodiagnostics. Two main actors are involved in the approval of drugs and pharmacodiagnostics. At a European level, there is the European Medicines Evaluation Agency (EMEA). At a country level, there are different national regulatory agencies. In the UK, there is the Medicines and Health Care products Regulatory Agency (MHRA) and in Spain, AGEMED (Agencia Española de Medicamentos y Productos Sanitarios).

3.2.1 The Approval Process: the EMEA

Medicines in Europe have been approved, since 1995, by the EMEA, a de-centralised body within the European Union. The EMEA has a two-track authorisation system:

- A centralised system through which companies gain marketing approval valid in all European Union (EU) and EEA-EFTA (European Economic Area – European Free Trade Association) (Iceland, Liechtenstein and Norway) states. A number of products can only be approved through the centralised procedure:
- Therapeutic (but not diagnostic) products derived from biotechnology and other high-technology processes.
- Human medicines intended for the treatment of HIV/AIDS, cancer, diabetes, neurodegenerative diseases, auto-immune and other immune dysfunctions, and viral diseases.
- Orphan medicines intended for the treatment of rare diseases.

For the products that do not fall under those categories (e.g. generic drugs), countries can go through the de-centralised procedure (EMEA, 2009).

- The de-centralised system is where companies can ask for marketing approval for individual countries and, once it is obtained, can request other member states to recognise the same authorisation. The procedure is also known as "mutual recognition". Although the de-centralised procedure is the responsibility of national

regulatory agencies, the EMEA's main evaluation group, the Committee for Proprietary Medicinal Products (CPMP) (a technical group formed by 30 members), still has a formal role in the decentralised procedure by arbitrating between member states in cases where there are disputes over granting authorisations. Also, the EMEA's Mutual Recognition Facilitating Group (MRFG) helps national agencies to overcome possible disagreements among countries (Garattini and Bertele, 2004).

During the approval process drugs can be refused because of lack of clinical validity, and after the approval process they can still be rejected because of safety problems.

However, the EMEA, unlike the US Food and Drug Administration (FDA), is not involved in the approval of pharmacodiagnostic tests since it only focuses on therapeutics. The EMEA does not assess any diagnostic test for PGx use, although it has, since 2002, had a PGx Working Group (PGWP) (later the PGx Expert Group) that gives assistance on post-marketing authorisation procedures for relevant PGx (see figure 3.1). The EMEA also collaborates with national authorities in the assessment of the clinical utility of PGx, although the approval of pharmacodiagnostics is the responsibility of national regulatory agencies such as the MHRA in the UK or AGEMED in Spain. The EMEA, together with the FDA, also encourage pharmaceutical companies to submit PGx information associated with new drugs through the voluntary genomic data submission scheme (VGDS), even if such information is not used for drug approval (FDA, 2004b).

The separation of assessment responsibilities between the EMEA and the member states in regards to pharmacodiagnostics and PGx, raises some concerns (Hopkins et al., 2006), and the EMEA, aware of this, is enhancing the channels of communication with the national diagnostics authorities and is including PGx data in the technical documents that relate to PGx testing.

3.2.2 Granting UK Licenses: the MHRA

The Medicines and Health Care products Regulatory Agency (MHRA) is the body responsible for medicine regulation in the UK. Since 2003 the MHRA has regulated both medicines and medical devices.

The primary legislation regarding medicines in the UK is the Medicines Act 1968, although most regulatory legislations emanate from Europe. Before a medicine can be sold in the UK, a number of licences are essential: the product itself must have a licence called a "marketing

authorisation" (formerly called a "product licence") and companies that are involved in all stages of the manufacture and distribution of the product also need to have a licence. Applications for clinical trial authorisations and marketing authorisations are assessed by medical, pharmaceutical and scientific staff at the MHRA.

Safety, quality and efficacy are the only criteria on which legislation to control human medicines is founded. It is the responsibility of the MHRA and the expert advisory bodies set up by the Medicines Act to ensure that the sometimes difficult balance between safety and effectiveness is achieved. MHRA experts assess all applications for new medicines to ensure they meet the required standards. This is followed up by a system of inspection and testing which continues throughout the lifetime of the medicine. Safety monitoring is also continuous and the MHRA also ensures that doctors and patients receive up-to-date and accurate information about their medicines. This is achieved by ensuring that product labels, leaflets, prescribing information and advertising meets the required standards laid down by the regulations (MHRA, 2009b).

3.2.3 Drug Monitoring and Post-Marketing Surveillance

Even after market approval, some drugs get rejected because of a lack of efficacy. Patients can remain susceptible to not responding to a drug or developing adverse events, and this is partly the consequence of drugs being developed without a full understanding of their mode and their site of action (Skyes, 2000). Therefore, when a drug reaches market approval, it still needs to go through a process of post-marketing surveillance where the sponsoring company looks for long-term adverse events that could not be observed earlier on in the process, because the evidence required for marketing approval is based on a generalisation of the results of clinical trials which may misrepresent the real adverse reactions. Post-marketing surveillance in the UK is the result of a collaboration between pharmaceutical companies, clinicians and patients, who can report unexpected ADRs through the Yellow Card Scheme, a system run by the MHRA that monitors the safety of the medicines that are on the market and enables the reporting of these ADRs, as well as the management of the drug safety updates. However, since the Yellow Card Scheme reports are made on the basis of suspected, rather than confirmed, side effects of medicines, it is not possible to draw definitive conclusions on the safety of drugs on the basis of Yellow Card reports alone, without further scientific evidence (MHRA, 2009c). All reports made to the MHRA on suspected reactions to drugs are listed in the MHRA Drug Analysis Prints (DAPs), which give a complete listing of all

UK spontaneous suspected ADRs reported through the Yellow Card Scheme. If a new side effect is identified, information is carefully considered in the context of the overall side effect profile for the medicine and how it compares with other medicines used to treat the same condition.

The MHRA will take action, if necessary, to ensure that the medicine is used in a way that minimises risk, while maximising patient benefits. Such changes may include the restriction of an indication or special warnings and precautions. Rarely, a drug may need to be withdrawn from the market, if the risk of side effects is considered to outweigh the benefits of treatment (MHRA, 2009a). Drugs are usually withdrawn from the market by the EMEA, who, every five years, review whether drugs can remain on the market (see Figure 3.1). If a drug has no record of serious adverse effects, market authorisation renewal should be automatic (Garattini and Bertele, 2004).

3.2.4 Regulating Pharmacodiagnostics: the IVD Directive

The In-Vitro Diagnostic (IVD) Medical Devices Directive 98/79/EC of the European Parliament of 17 October 1998 (EC, 1998) sets the basis for the commercialisation of in vitro diagnostic devices, which include genetic as well as other types of diagnostic tests. The IVD Directive was implemented in UK legislation by the Medical Devices Regulations 2002, and came into force on 13 June 2002. The directive, together with other medical devices regulations, came into full force on 7 December 2003, although IVD tests that were already in the distribution chain could continue to be supplied for two years until 7 December 2005 (MHRA, 2006).

The directive introduced common regulatory requirements dealing specifically with the safety, quality and performance of IVD medical devices and, under this regulation, any test aiming to get market approval would need to satisfy these requirements. In Europe, the validation of IVD tests resides in national authorities (and not the EMEA, as with drugs) which undertake an evaluation called "conformity assessment" that looks into the parameters stated by the IVD Directive (quality control, labelling, reagents and sterilisation of the clinical material). In the UK, the body notified to do this is the MHRA, although any manufacturer from the UK can request a conformity assessment from any other EU notified body as these devices are commercialised within the EU territory.

An IVD is defined as "any medical device which is a reagent, reagent product, calibrator, control material, kit, instrument, apparatus, equipment or system, whether used alone or in

combination, intended by the manufacturer to be used in vitro for the examination of specimens, including blood and tissue donations, derived from the human body, solely or principally for the purpose of providing information: concerning a physiological or pathological state; concerning a congenital abnormality; or to determine the safety and compatibility with potential recipients, - or to monitor therapeutic measures".

There are four categories of IVD tests under the directive: the first category covers products to screen the blood, the second and third are self-test devices that require less intervention and the fourth is defined as "self-declaration", because the manufacturer has to prepare a technical file for the product, which lists how it meets the essential requirements of the IVD Directive. Pharmacodiagnostic tests lie within this category.

In order for a diagnostic test to be commercially available it needs to provide satisfactory information about safety and efficacy that could include the diagnostic reagents used in the assay, the labelling of the kit, the sampling procedures, the sterilisation techniques or the nomenclature used for the purpose of regulatory data exchange. This requires a high investment in clinical trials by diagnostic companies who often do not have the necessary resources. One of the possibilities that PGx offers is the possibility of developing commercial diagnostics, possibly through collaboration with pharmaceutical companies interested in co-developing drugs and tests, provided the necessary drug-test associations can be translated into technical instruments. However, one of the main weaknesses of IVD tests is the lack of standards of clinical utility, which is a crucial element in assessing the potential of the test for improving relevance in clinical practice. At the moment, without such standards, the introduction of diagnostic tests into the clinic occurs without much evidence of clinical utility.

The market for diagnostics is rather small (in 2007, the average IVD sales in most European countries represented less than 1% of the total health care expenditure, with €9,685 million of sales) (European Diagnostic Manufacturers Association, 2008), but this trend may change if the demand for testing increases heavily and if eventually, in the future, PGx becomes "wholesale".

3.2.5 IVDs and Gene Patenting

Since 1949, the UK Patent Office has stated that the first person to discover and isolate a natural substance could be granted a patent. Under the current US and European patent system, genes are discoveries, since they already exist in nature, and are therefore not

inventions; they cannot be patented unless they are found to have a useful application (whether or not the genetic function has been discovered). Since 1998, the European Directive EC Directive 98/44/EC has claimed that "an element isolated from the human body or otherwise produced *by means of a technical process, including the sequence or partial sequence of a gene, may constitute a patentable invention, even if the structure of that element is identical to that of a natural element"* giving the owners of gene patents control over the way in which the knowledge of the genes is used. According to some clinicians, this leaves public laboratories rather unprotected (respondent 23).

These claims and the idea that a gene or DNA sequence can be the subject of intellectual property rights (IPRs), and be part of an invention, has attracted increasing criticism. Some people, researchers in particular, feel uncomfortable with the idea that genes and other DNA sequences can be used for commercial gain. The clinical community is also concerned about the impact of patents on genetic testing services[4], which may increase their prices and put public service delivery at risk, because a patent on genetic sequence can prevent laboratories from using that genetic sequence.

One of the main disadvantages perceived by some of the interviewees was that, with the introduction of commercial genetic tests, prices for testing will rise, because public laboratory always charge less for doing a test than a company (respondents 1, 13 & 23). One of the arguments against the delivery of diagnostic tests by private companies is that, once they have been granted the patent on a test or DNA sequence, they will be interested in getting as much benefit from that patent as they can. Then, the pressure to improve the existing technologies and the protocols for testing would be reduced because they have already got a patent and they would rather exploit that patent for the highest economic benefit, rather than start investing in new innovations. On the other hand, researchers believe that public laboratories, who are continuously interested in finding better ways of diagnosing and treating disease, would work on improving protocols and testing procedures. Under this perspective and, if the genetic patent system does not change, public laboratories may face situations in which they might need to pay royalties to the diagnostic companies commercialising genetic tests, in order to deliver service at the NHS.

[4] A patent lasts for 15 years and more if it is extended.

Therefore, while patenting remains as a form of protecting inventions, the main point of concern for researchers and public service providers is how much patent protection can affect public service delivery? In the case of gene patenting, these concerns are accentuated, because "owning" a genetic sequence grants rights of exploitation of that genetic sequence in a number of different forms of testing, so it is not only one gene and one test, but different possible tests, available from a genetic sequence.

3.2.5.1 Research Use Only (RUO) Tests

There are a series of products designated for Research Use Only (RUO), which are out of the scope of the IVD Directive and cannot be targeted for clinical use. These tests are used for basic research, pharmaceutical research and market studies, for the identification of substances in biological specimens or during in-house manufacturing of so-called "home-brew" tests. Some of these tests are commercially available and can be sold to research laboratories or other business but they can also be non-commercial, such as "home-brew" or laboratory developed tests (LDTs), in which case it is a laboratory who delivers a test by combining reagents and following specific protocols (EC, 2004).

3.2.5.2 "Home-Brew" or Laboratory Developed Tests (LDTs)

When a company cannot develop a test because of the high costs of clinical trials or when a hospital laboratory considers that the test offered by a company is too expensive, then it would look for a similar non-commercial alternative or "home-brew" test.

"Home-brew" or laboratory developed tests (LDTs) are non-patented tests done in a laboratory by mixing reagents and following protocols and, in contrast to IVD tests, they are not regulated by the IVD Directive. For "home-brew" tests it is enough that a laboratory complies with sufficient standards of quality to be able to offer assays made in-house, similar to commercial tests.

The problem with "home-brew" tests is that, if a company owns the property rights for a specific test similar to a "home-brew" one, then the company could ban the laboratory from doing a similar "home-brew" test, because, while the company's IVD test holds intellectual property rights, "home-brew" tests do not. Alternatively, the company could license the

commercial test to the laboratory[5] instead of imposing a ban, because the laboratory that is already running the testing has created a market for it and the private company could benefit from this in order to enter into a local market.

3.2.6 A New Patent Convention

In the light of the fears that gene patenting posed, the Parliamentary Assembly of the Council of Europe considered the need for a new Patent Convention revisiting the concept of patenting living matters, and this included genetic sequences. The Parliamentary Assembly of the Council of Europe claimed that, if there was a patentable property, it should be public and not private (Nuffield Council on Bioethics, 2003). Nevertheless, at present, anybody isolating any functional DNA sequence still has the right to ask for a patent and, despite this is a big issue for some groups of researchers and clinicians, patenting genetic sequences is being the business strategy adopted by some companies like Myriad Genetics.

In the future, it is unclear whether the existing Patent Convention will be revisited. If it was, and if genetic sequences became "non-patentable", then, companies like Myriad Genetics would not have such strong incentives to develop diagnostic tests as they would not have market exclusivity. In that case, it could be possible that the development of genetic testing services would be shifted to public research and clinical laboratories.

3.2.7 The Legal Framework for Drug-Test Approval and Labelling

The link between diagnostics and drug prescription is only possible through the development of diagnostic tools capable of correlating information on genetic/phenotypic biomarkers with drug response, and this requires a stringent regulatory framework. However, the co-development of drugs and tests often faces some challenges: the legislative frameworks that apply to drugs and diagnostics are not always the same. While drug approval applies at a European level, the approval process for diagnostics applies at a country level, so the EMEA in Europe is not allowed to co-approve drugs and pharmacodiagnostics, unlike the FDA in the US. Nevertheless, while the EMEA cannot approve diagnostic tests, in the summary of the product characteristics (where PGx data is available) the EMEA can change the labelling of the drug when a new PGx indication becomes available (any EU member state can request a

[5] Myriad Genetics for example licensed its BRAC tests to a German company (BioSciencia®) so that BioSciencia® could use Myriad tests in Germany.

change to the labelling of approved products if new PGx data becomes available). For example, the label for the anticancer drug Irinotecan (*Campotosar®*, Pfizer) was changed after some patients treated with the drug suffered severe and prolonged neutropenia. This ADR had a genetic component and, while the EMEA did not approve the test for detecting these adverse events, it recognised the validity of the test in changing the drug label.

The possibility of updating the label with information that becomes available post-marketing is a key argument for introducing PGx, although the lack of coordination in the approval of drugs and tests at the European level represents an important weakness for PGx adoption and future service delivery (Hopkins et al., 2006). The EMEA is aware of the need to encourage PGx by developing formal channels of communication with the national diagnostics authorities and consequently has created a PGx Working Group (PGWP). However, until formal communication channels are put in place, PGx will not be implemented in a harmonised fashion across Europe, and there is a risk of this leading to disparities in pharmacogenetics service delivery across member states.

3.3 The Context of Health Service Delivery

3.3.1 Clinical Utility

The translation of any drug or instrument into clinical practice requires compliance with three criteria: the technical accuracy of the drug or device (analytic validity), its clinical sensitivity and specificity (clinical validity), and its potential for improving health outcomes (clinical utility). Other factors that are also taken into consideration when deciding whether a drug or device should be used in the clinic include: how severe the disease they intend to treat is, which treatments are already available, how accessible testing is, and other ethical, social and legal implications associated with its use (Shah, 2004).

There is no a clear definition of clinical utility; however, the term is commonly used as a synonym of clinical sensitivity, which, in other terms is a combination of clinical effectiveness and/or economic evaluation, accounting also for the practitioners' perspectives about the usefulness, benefits, and drawbacks of the innovation for their working practice (Smart, 2006). The safety and efficacy of drugs is assessed by the drug regulatory agencies, on the basis of the results of clinical trials (that prove the analytic and clinical validity as well as the safety of the drug), submitted by pharmaceutical companies. Once a drug is approved, its

cost-effectiveness is evaluated, in the case of the UK, by NICE, who decides whether the product should be reimbursed by the NHS. Finally, the practitioners' perspectives on the use of new drugs are received through the clinical profession. The combination of the three plays an important role in deciding whether a new drug reaches the adequate standards for clinical implementation and, eventually, also reimbursement. For this reason, the term of "clinical utility" will be used all along the thesis.

3.3.2 Regulating Clinical Practice

Good Medical Practice refers to the principles and values on which good practice is founded. It is addressed to doctors but is also intended to let the public know what they can expect from doctors. In the UK there are three bodies of knowledge involved in setting up guidance for good practice:

1. The General Medical Council (GMC) dictates what good medical practice means, and has a statutory role towards doctors and provides guidance on medical ethics. The GMC regulates doctors who practice in the UK, so all of them need to be registered with the GMC. The guidance established by the GMC is expected to be followed by any doctor registered in the UK, whether in public or private practice. Even though it is not statutory, failure to follow its principles can put registration at risk.

2. The National Institute of Clinical Excellence (NICE) is an independent institution within the Department of Health (DoH) that provides national guidance and recommendations on ways to promote health through technology appraisals of specific treatments, as well as public health guidance. NICE is unable to provide guidance on all treatments and so it prioritises those treatments which they anticipate may have clinical relevance, either by providing a considerable health benefit and/or by being highly cost-effective. NICE often relies on the input of technologies provided by the National Horizon Scanning Centre (NHSC) at the University of Birmingham, which is a member of the International Information Network for New and Changing Health Technologies (EuroScan International Network). The NHSC *provides advanced notice to the UK's Department of Health and national policy makers, including NICE, of selected key new and emerging health technologies that might require evaluation, consideration of clinical and cost impact or modification of clinical guidance prior to launch on the NHS* (National Horizon Scanning Centre, 2009).

The role of NICE is make sure that the standard of practice is consistent across the NHS, suggesting what the best practice should be and who should pay for it. All doctors and staff within the NHS are expected to follow NICE guidelines. Since January 2002, the NHS has been legally obliged to provide funding and resources in England and Wales for medicines and treatments recommended by NICE, implying that NICE guidance and clinical guidelines are of a statutory character. Once a guideline has been released, NHS Trusts need to implement it within the following 3 years after their release. In non-NHS settings, NICE guidance does not apply because the NHS reimbursement policies do not apply.

3. Clinical Associations are organised groups that represent the medical profession, which, by exchanging knowledge through publications, seminars and conferences, set particular clinical recommendations for the medical profession, on the grounds of what the clinical committees think is "good enough" clinical evidence. These recommendations are not mandatory, although peer opinion is a strong driver for clinical practice and, in particular, in cases where NICE does not say anything about a particular treatment or therapy, clinicians tend to follow their peers' recommendations. The clinical profession plays an important role in service delivery because clinicians are often the first users at the point of service delivery, acting as the gatekeepers of new treatments.

The clinical profession gathers around bodies of practice that evaluate drug delivery mechanisms and associated health care services in the context of good medical practice. They make clinical assessments and deliver recommendations and guidelines aimed at reinforcing good medical practice for a particular clinical profession. While these clinical guidelines are not mandatory, they are generally taken as a standard of practice among a particular community of practitioners, since they are considered a reference of clinical practice among their peers. However, not all clinical associations agree on the utility of new treatments, but the ones who do act as lead users for those particular treatments.

3.3.3 NICE and the Rationing of Service Provision

The introduction of medical technologies into clinical practice has always been contested, in particular in a public health care system like the NHS. The need to strike a balance between NHS expenditure and health outcomes, and the development of rational mechanisms to decide which medical technologies should be implemented into clinical practice, caused the UK Government to create a series of national agencies dedicated to assessing new therapies and technologies to ensure a good quality of care. In the light of these needs, NICE emerged

in 1999, to provide evidence-based guidelines through health technology assessments and cost-effectiveness studies, which health professionals and the organisations that employ them would need to take fully into account when deciding which treatments to reimburse.

The Health Service Circular 1999/176 set out the initial work programme for NICE, to give guidance to the NHS in three areas (NHS Executive, 6 August 1999): the appraisal of individual new and existing health interventions; clinical guidelines giving best practice advice; and clinical audit methodologies.

NICE issues various different types of guidance (NICE, 2008a):

- Public Health Guidance, which NHS organisations should take into account when they develop local agreements.
- Clinical Guidelines: NHS organisations should review the current management of clinical conditions and consider the resources and time needed to implement them.
- Technology Appraisals: NHS organisations should fund and resource the medicines and treatments recommended, usually within three months of NICE issuing guidance.
- Interventional procedures: NHS organisations should check whether NICE has issued guidance before carrying out a new procedure. If NICE has **not** issued guidance, then approval needs to be sought from their NHS Trust's clinical governance committee and they need to ensure that the patient has given informed consent before the intervention is used.

NICE has a pragmatic view on how decisions should be made, focusing on evidence: NICE uses a standard and internationally recognised method to compare different drugs and measure their clinical effectiveness: the quality-adjusted life year's measurement (the "QALY"). The QALY method helps measure these factors so that we can compare different treatments for the same and different conditions. A QALY gives an idea of how many extra months or years of life of a reasonable quality a person might gain as a result of treatment (particularly important when considering treatments for chronic conditions). Cost-effectiveness is expressed as "£ per QALY". Each drug is considered on a case-by-case basis. Generally, if a treatment costs more than £20,000-30,000 per QALY, then it would not be considered cost effective (NICE, 2009). But NICE's "narrative of evidence" often contrasts with the "narrative of politics" provided by the manufacturers whose drugs are being

appraised, and by clinicians, patient associations and the press. So it is not only evidence that drives reimbursement decisions, but also the dilemma between the evidence and the "politics" of personalised medicine (Hedgecoe, 2004). So, the evidence obtained through clinical trials is not always "good enough" for clinical implementation and the informed decisions of clinicians are often challenged by health regulators and administrators.

3.3.4 PGx Service Delivery

In April 2001, the Government announced a new investment of £30 million to develop specialised genetics services and, two years later, the interest in genetics was harnessed with the release of a White Paper (DoH, 2003), in which the government recognised the potential of genetics for improving health care, and announced an additional investment of £50 million in England to develop genetics knowledge, skills and provision through the NHS.

At present, PGx testing services are offered in some localities where there is expertise in it. However, PGx may have something to learn from the genetic testing services for breast and ovarian cancer in the UK. Two elements played a key role in this:

- The setting up of 26 Regional Cancer Screening Centres; and
- NICE guidance that recommended regular breast/ovarian cancer screening.

However, the situation for PGx is different. PGx is already being applied in a few cases, where specific genetic tests can determine susceptibility to drugs like trastuzumab (Herceptin®) in breast cancer, imatinib (Gleevec®) in chronic lymphoblastic leukaemia or ziagen (Abacavir®) in HIV, but there is not yet an established pattern of PGx service. The way PGx services are offered at the moment depends on the availability of the drug, the test, whether NICE approves them and whether any laboratory offers testing, although the National Genetics Reference Laboratory (NGRL) is looking into models that might lead to such a diagnostic service.

A model proposed for cancer therapy (Dalton and Friend, 2006), which may also have implications for PGx, suggests that the inclusion of molecular genetics in cancer treatment could be represented by a cycle of discovery-translation-delivery. Here, the discovery of specific molecular alterations in tumours would be followed by the establishment of linkages between genetic alterations and patient outcomes in clinical trials and, once this relation of

genotype to clinical outcome was found, it could then be translated into clinical practice. However, two important challenges emerge from this model:

- How to establish a consistent relationship between a patient's genetic alteration and his or her outcome.
- How to translate this into the clinic, in a system driven by clinical evidence and cost-effectiveness studies, where changes in service delivery are highly controlled by clinical gatekeepers.

Based on the weaknesses of the clinical trial and post-marketing surveillance process that lead to a number of ADRs after drug approval, a model proposed by Davis and Khoury (2006) suggests that the assessment of the safety and effectiveness of drugs, carried out during clinical trials, should not be decisive (see Figure 3.3). They suggest that instead, after the trial finishes, there should be a continuous process which would require a more systematic evaluation, based not only on a record of the adverse drug reactions that occur during post-marketing surveillance, but also of the genetic responses of patients to drugs, which will continuously feed back into clinical practice.

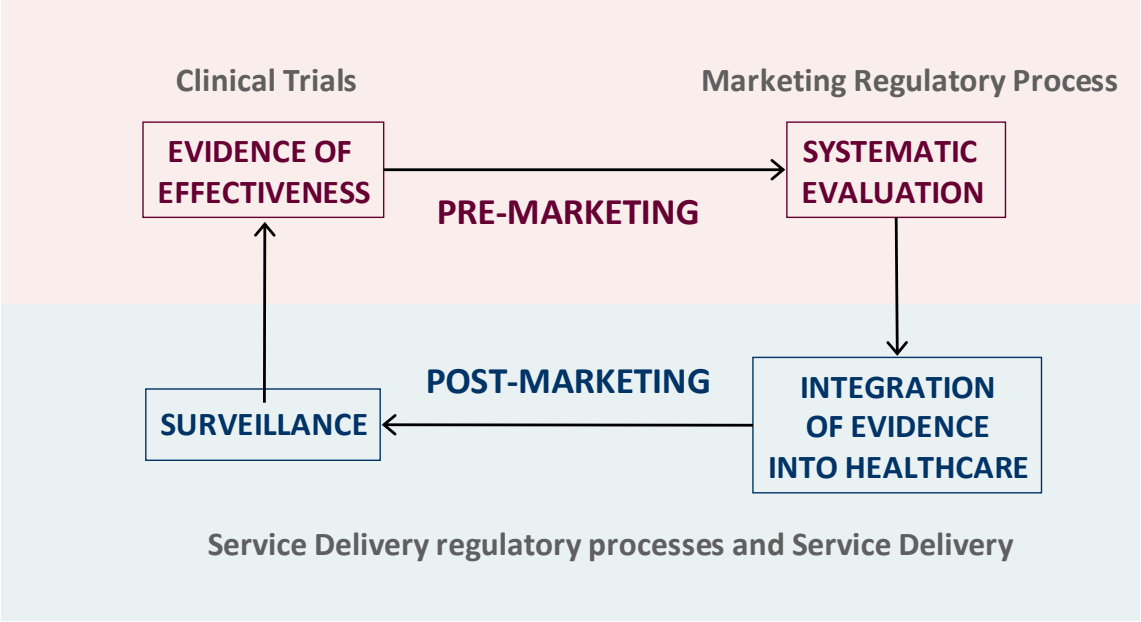

Figure 3.3: Public health approach for PGx gene-based diagnostic tests of Davis and

3.3.5 Evidence Based Medicine

Evidence Based Medicine (EBM) was established in 1992 in an effort to establish a more systematic way of treating disease (Evidence Based Medicine Working Group, 1992). EBM looks at the clinical evidence of new treatments, as a result of informed decisions about

clinical safety and efficacy, usually proven through the process of randomised controlled trials, although not exclusively (Klein, 2001).EBM is defined as *the enhancement of a clinician's traditional skills in diagnosis, treatment, prevention and related areas through the systematic framing of relevant and answerable questions and the use of mathematical estimates of probability and risk* (Greenhalgh, 2001), or as "the conscientious, explicit and judicious use of current best evidence in making decisions about individual patients" (Heneghan and Badenoch, 2002) p. 2. EBM, therefore, focuses on minimising risk, such as the risk to new procedures or the lack of awareness among professionals of new studies and treatments. EBM looks for outcomes of clinical trials and medical studies, although these need to be adapted to the patients, as there are often differences in the outcomes that are relevant to patients and the outcomes obtained in these studies (Heneghan and Badenoch, 2002). The dilemma consists in understanding how appropriate a specific study is for a specific group of individuals and not for another and how efficient would a specific drug be for one patient and not for another (Greenhalgh, 2001).

Some of the weaknesses of EBM lie in the fact that, the level of uncertainty of new medical technologies is high when these are introduced into clinical practice, because the full range of information on a technology's effectiveness cannot be expected to emerge in clinical trials that are designed to test a narrowly defined set of clinical benefits (Gelijns et al., 2001).

Uncertainty is an inherent element to both the occurrence of disease and the effectiveness of treatments. For this reason, medical innovation involves great uncertainties that require reliance upon information that can only be generated by studies and clinical experience. The resolution or reduction of uncertainty in these cases occurs through "applied" learning in clinical practice, or, in other words, trial and error or learning-by-using experiences (Gelijns et al., 2001). In this sense, it is not well established how much of the evidence obtained through randomised controlled trials and how much of the learning-by-doing experiences, clinical practice should rely upon.

3.4 Architecture of the Health Delivery System: The Institutional Context

This section aims to provide some notions about the institutional context in which PGx is delivered.

Institutional arrangements are defined as administrative rules, norms, laws and conventions that society uses to legitimize, regulate and coordinate the actions and expectations of individuals (Van de Ven et al., 1999) (p. 151). Individuals and organisations become institutional actors by exercising the institutional roles they assume or are assigned. In this way, institutional arrangements have created roles for these individuals and organisations, such as firms, trade associations, state agencies or markets.

Institutional arrangements are important in innovation studies, to the point that, success of failure of technological innovation is, in great measure, a reflection of the institutional arrangements and available resources that a community needs to sustain its members (Freeman, 1986). Therefore, the institutional arrangements that influence how medical innovation emerges and is transferred into clinical practice, will provide the framework to undertake a macro analysis about the use of PGx in drug development and service delivery, taking into account, how firms (pharmaceutical and biotechnology companies in this case) develop new PGx technologies, but also, how public and private sector actors perform critical functions to develop and commercialise these new technologies.

The following sections will deal with two main institutional settings: the Health Care State and the Health and Pharmaceutical System. These, at the same time, include the institutional actors such as (NICE, the GMC or the different clinical associations) we have referred earlier on in the chapter in sections 3.2 "Special factors relating to PGx: Marketing Pharmaceuticals" and 3.3 "The Context of Health Service Delivery".

3.4.1 Governing the Health Care State

The Health Care State refers to governing and governing involves the state shaping health care institutions, but also the health care institutions shaping the state. There are three main political arenas which the Health Care State demands that it governs (Moran, 1999: pp1-12):

Governing Consumption or the conditions under which populations have access to health care services. Consumption has a collective character because it is collectively financed and its access is collectively regulated and it frequently acquires organised forms (e.g. patient organisations, insurance subscribers); these are important institutional actors in the health care system and service delivery. However, consumption is dominated by cost-containment, the reason why the dominant theme of health care policy in recent years has been governing the total cost of consumption of health care services.

Governing Professionals: professions and concentrations of expertise, which are central to the health care system but who use the strategy of professionalism to defend their own occupational interests. So, at the same time that professional groups retain expertise, this expertise is used as a way to legitimise their ideologies and occupational interests, mainly because doctors have hierarchies in the health care system and the state has made them a centerpiece of health care policies. Because doctors have been on the receiving end of state power they have been involved in the development of the Health Care State. As an example, the British Medical Association (BMA) is a professional group with great influence over policy-making, which is evidence that health care institutions are shaped by the state (the government reshapes the systems for governing the medical profession). Other institutions also shape some features of the Health Care State (doctors emerged as the managers of the consumption process). Consumption and professional organisation are, in the main, defined by national boundaries

Production Politics or the inter-connection between the health care system and the industrial economy. The application of basic and applied science to clinical care has created modern health care systems and has generated associated industries. Medical technology is reliant on the artefacts of modern technology (e.g. scanners, blood pressure machines or pharmacodiagnostics) and these connect the heath care system with the industrial economy, hence place medical technology within the Economic State. So, the politics of technological production are positioned within the wider politics of industrial production and both are embedded within the politics of the industrial system. Therefore, the Economic State is being shaped by but also shapes the wider Health Care State.

The introduction of PGx and personalised medicine into clinical practice will then depend, to a great extent, on the balance between the industrial dynamics that are at the root of PGx innovation and the adoption of the technology by health care professionals.

3.4.2 The UK Health & Pharmaceutical System

UK health care is dominated by a policy mix. First, a command-and-control mechanism represents policy-makers who rationalise health care services through priority-setting. The command-and-control system sets an overall budget, based on taxation and a subsequent

allocation of resources.[6] In contrast to the policy-makers, the clinical profession retains control over its own work and acts as gatekeepers of treatments and therapies. Doctors, through professional networks, have a large amount of power through their self-regulation and are accountable for their own work and that of their peers. In past years, the increased number of consultations with the public launched by the UK DoH, has demonstrated a move towards a more pluralist approach to health care. However, despite these efforts, major policies have still been implemented with little consultation with the public, patients or patients' advocates (Williamson, 2008). Defenders of the command-and-control system claim the importance of rationalising health care delivery so that there is equal access. Most critics, however, argue that setting an overall budget has harmful effects, because the tendency to stay within the budget often lowers standards instead of improving efficiency (Green, 1998) and, one of the main implications is that the medical profession is often obliged to select treatments accommodated to the budget constraints set by the health care managers.

The introduction of PGx into clinical practice will, then, face the lack of consensus between health care rationalisers and practitioners.

The main actors involved in drug regulation are:

- The Medicines and Healthcare products Regulatory Agency (MHRA), who approves therapeutics and diagnostics at a country level.
- The National Institute of Clinical Excellence (NICE) which was established to produce national guidance on specific health technologies including both medicines and medical devices (through its Technology Appraisal process) and clinical practice (through its Guidelines development process). Since January 2002, it has been a mandatory requirement for NHS organisations in England and Wales to provide funding for medicines and treatments recommended by NICE in its Technology Appraisal guidance.
- NHS Foundation Trusts, which decide, locally, which treatments should be implemented at a local level, in particular in the absence of a clinical guideline.

[6] The NHS receives most of its funds from general taxation, with the remainder coming from national insurance contributions and prescription charges.

Once a drug has been approved by the EMEA and the MHRA, NICE and the DoH are also involved in the pricing of drugs and can influence the growth of drugs already on the market (see Figure 3.4). NICE evaluates whether:

- a technology is likely to provide a significant health benefit across the NHS;
- a technology is likely to have a significant impact on other health related government policies (e.g. a reduction in health inequalities);
- a technology is likely to have a significant impact on NHS resources (financial or other) if given to all patients for whom it is indicated;
- the Institute is able to add value by issuing national guidance.

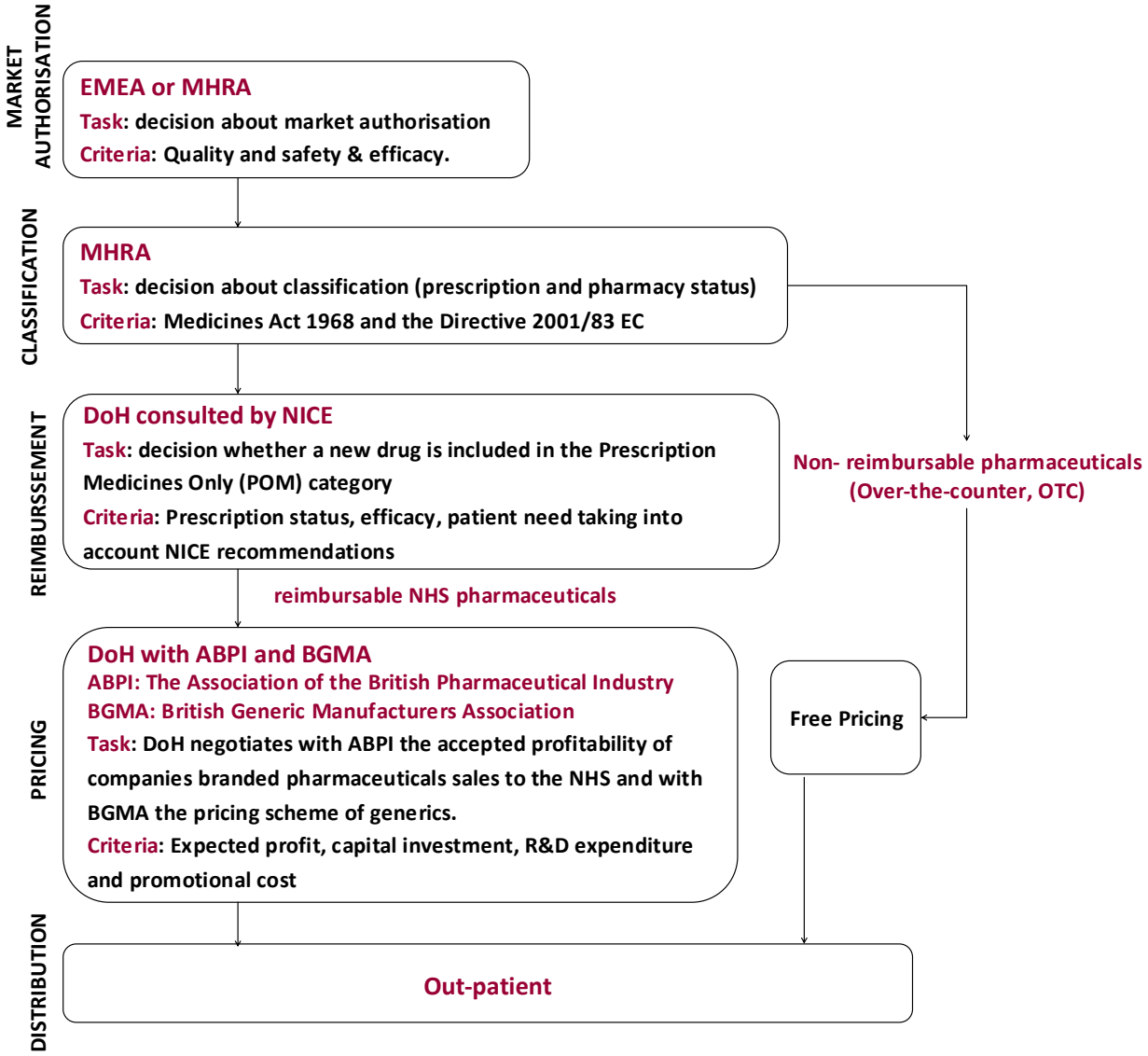

Figure 3.4: The UK Pharmaceutical System (Habl et al., 2006)

3.4.3 The Spanish Health & Pharmaceutical System

The Spanish health system (Sistema Nacional de Salud – SNS) is similar to the UK health care system, a public regime based on taxation, coordinated and supervised by the Ministry of Health (Ministerio de Sanidad y Consumo - MSC). However, contrary to what happens in the UK, the system is decentralised into seventeen autonomous regions. The MSC focus on pharmacovigilance, product approvals, cost-containment and long-term policies, while each region is responsible for health care delivery and finance.

When marketing authorisation is granted either by the European Medicines Agency (EMEA) or the Spanish Medicine Agency, AEMPS (Agencia Española del Medicamento y Productos Sanitarios), the MSC initiates a procedure to decide on the reimbursement of this new product as part of the national reimbursement list (see Figure 3.5). The manufacturer is then invited to provide all relevant information to allow the Inter-Ministerial Pricing Commission, CIPM (La Comisión Interministerial de Precios de los Medicamentos), led by the MSC, to make a decision. If the outcome is positive (resulting in inclusion in the national reimbursement list), this decision is valid (i.e. mandatory) throughout the country. There are three reimbursement categories:

- 100% reimbursement for hospital pharmaceuticals;
- 90% reimbursement for pharmaceuticals for the management of chronic illnesses (e.g. diabetes, asthma and epilepsy);
- 60% reimbursement for the majority of prescription-only pharmaceuticals.

Although Spanish pharmaco-economic guidelines are available going back to 1995, these types of studies do not have to be used in the pricing and reimbursement process (ISPOR, 2009).

The Spanish health system also has a national agency that evaluates drugs and medical technologies, AETS (Agencia de Evaluación de Tecnologías Sanitarias). The role of the AETS is to promote the adequate use of existing drugs to improve the quality of health care, although it has more of a consultative role than NICE does in the UK. Most AETS reports are initiated by a request, usually from a government or government-related office. These reports are reviewed by an independent panel of experts who endorse the conclusions.

In four regions (Madrid, Catalonia, the Basque Country and Andalusia), there are also regional evaluation agencies who are involved in the process of technology implementation within that region. This leads to differences across regions, with the most innovative allocating more resources to healthcare and facilitating the introduction of new medical technologies, although the fact that the tax associated with health is the same in all the regions.

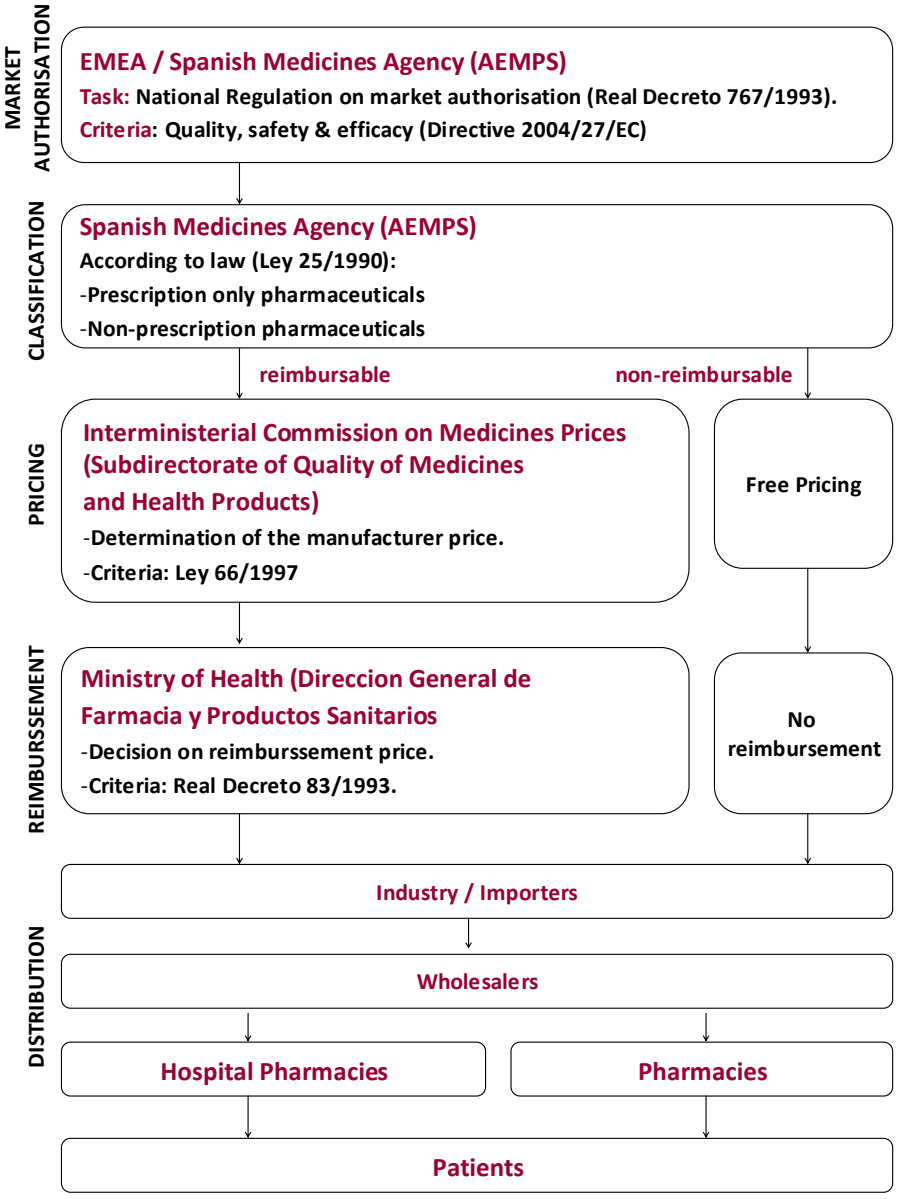

Figure 3.5: Spanish Pharmaceutical System (Habl et al., 2006)

3.5 Summary

The purpose of this chapter was to present PGx in the context of drug development and service delivery, focusing on the aspects that underlie research and development, drug regulations and in general, healthcare governance. This chapters serves to place PGx in a context under which further discussions (see chapters 8 and 9) will take place.

Part of the chapter is dedicated to explaining the functioning of the health system We presented along the chapter the processes which currently control health service delivery and how these influenced and were influenced by the introduction of PGx. We also dedicated part of the chapter to critical regulatory matters that PGx needs to face, as well as some ethical issues that have not yet been solved. At the end of the chapter we present two different health and pharmaceutical systems (the UK and Spain), where PGx is used, to set the basis of a comparison between how two different institutional settings influence PGx diffusion.

Chapter 4. Framework of approach to study and methodology

4.1 Research Purpose

Pharmacogenetics (PGx) is the study of the genetic differences in drug response among groups of individuals who share common genetic characteristics (Lindpaintner, 2003), determining how likely we are to react to drugs in terms of efficacy and toxicity, depending on the information contained in our genes (Evans and Johnson, 2001). The concept was first used by Henri Vogel in 1959 and later on applied by Werner Kalow (Kalow, 2002).

PGx and personalised medicine require the integration of gene/phenotypic diagnostic tests (pharmacodiagnostics) into clinical practice, so drugs can be delivered according to the results of these pharmacodiagnostics in order to either avoid ADRs caused by already licensed drugs (or "blockbusters") or prescribe new drugs ("minibusters") only to a specific genetic or phenotypic sub-population, known to respond to the drug.

The purpose of this chapter is to present the methodology used to investigate the translation of PGx from the development phase into service delivery, as well as conceptualising the research problem: why PGx and personalised medicine have not been widely implemented in clinical practice (see research questions in section 1.4). The conceptual framework presented here will, later on, be used in the discussion and conclusion chapters to analyse the factors that hamper the widespread use of PGx as well as inform policy options on how to improve PGx service delivery.

4.2 Implementation of the conceptual framework

In chapter 2 (see section 2.2), we introduced the concept of socio-technical systems and we recognised that techno-scientific knowledge is distributed across a wide range of social

groups and actors (universities, laboratories, consultancies, R&D units in firms) whose relationships constitute a socio-technical system that encompass production, diffusion and use of the technology. These systems do not work autonomously but are the outcome of the activities of human actors and social groups (see figures 2.1 and 2.2). These groups and individual actors build an infrastructure that facilitates and constrains innovation. This infrastructure includes (Van de Ven et al., 1999) p. 149: (1) institutional arrangements to legitimize, regulate and standardize a new technology; (2) public-resource endowments of basic scientific knowledge, financing mechanisms and a pool of competent labor; (3) development of markets, consumer education and demand; and (4) proprietary research and development, manufacturing, production and distribution functions by private entrepreneurial firms to commercialise the innovation for profit.

In our particular case (and following the numbers explained above) we would consider that:

- The health care state includes not only the settings that regulate clinical practice, but also the regulatory agencies that control the introduction of new drugs in the market.
- It refers to the funding mechanisms, both public and private that support basic and applied PGx research.
- It refers to how PGx is being used both in drug development (to co-develop drugs together with diagnostic tests) and in clinical practice, taking into account the hurdles that the introduction new technologies face and how, these are overcome, leading to the creation of new markets.

This point relates to how new PGx devices are produced are commercialised, focusing on the proprietary mechanisms that underpin the commercialisation of new drugs and tests. In summary, the study of these interacting elements, which together form a socio-technical system, together with the differing perspectives and emerging controversies that the use of PGx poses, aims to bring some light on why PGx is not widely used in clinical practice.

The main body of literature used to tackle the problem of this research has been diffusion of innovations theory in health service organisations (see section 2.3), where we aim to provide some insight on how PGx challenges current service delivery mechanisms.

In figure 4.1 we can see represented the socio-technical system under study. This system is divided in four major sections: the National Science and technology System, where we have placed the public laboratories doing basic research in PGx and associated technologies; the

Health Delivery System, through which drugs and testing services are delivered. Linking sub-systems, the pharmaceutical and biotechnology companies, who invest in R&D projects that have an origin in public basic research. These companies will then deliver new products to the health care system. Finally, the regulatory system that controls how drugs and pharmacodiagnostic tests are developed (focusing in their safety and analytical validity), and how they are delivered (taking into account clinical utility measures that include cost-effectiveness studies among others). A more detailed explanation of clinical utility is provided in section 3.3..1. The four sub-systems are interlinked, the National Science and Technology System cuts across the pharmaceutical and biotechnology industry, as well as across the Health Delivery System. The Regulatory System comprises both the development of drugs and pharmacodiagnostic tests, and the delivery of these through the Health System. Finally, institutions such as the Department of Health lie in the intersection of all the subsystems, since they are involved in the whole process of development and delivery of health services.

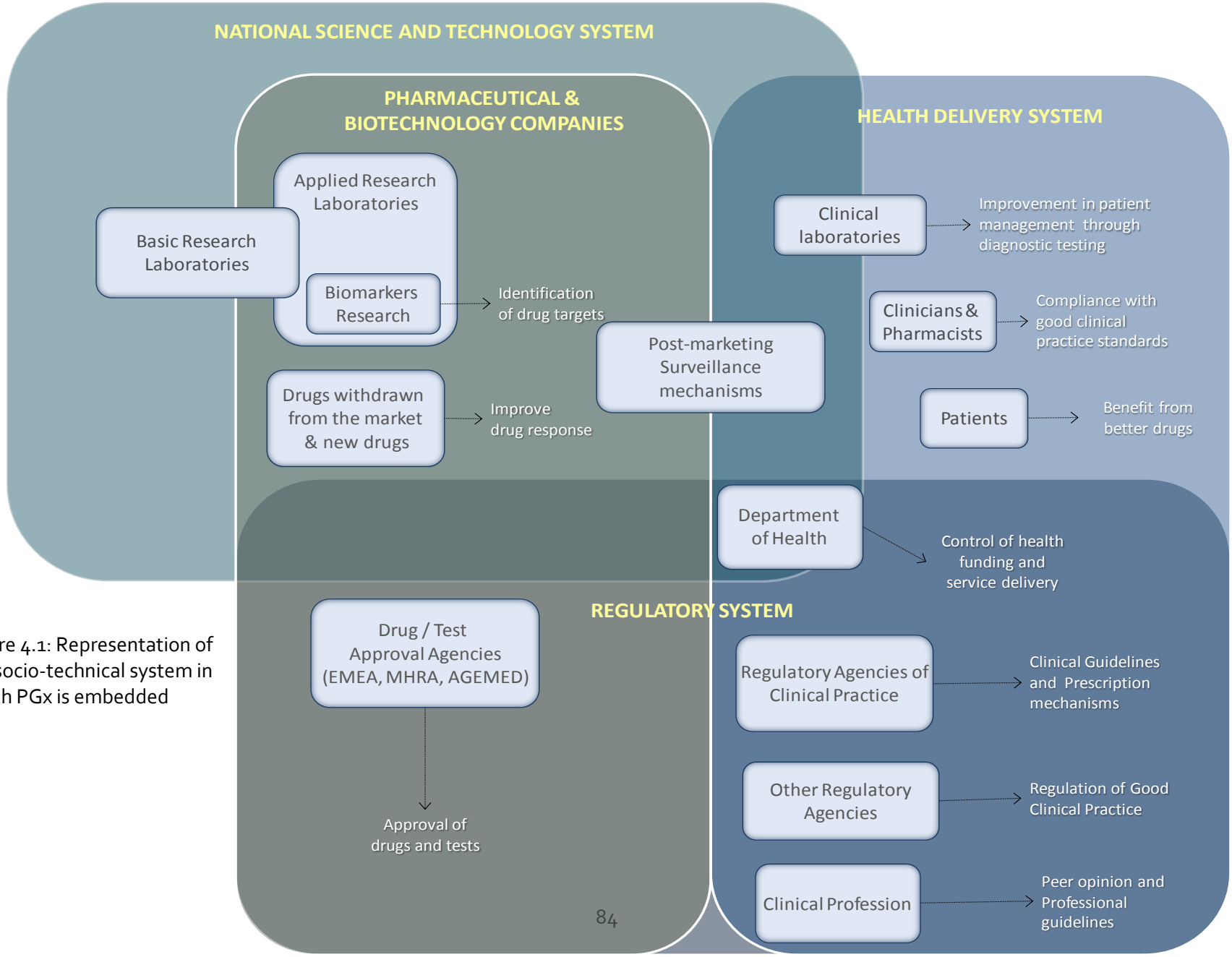

Figure 4.1: Representation of the socio-technical system in which PGx is embedded

4.3 Philosophical perspective

The epistemological stance of this research will lie in the school of thought named critical realism. A key premise in critical realism is that it accepts the existence of a reasonably stable and mind-independent reality but rejects the possibility of verifying research findings in any absolute or 'objective' sense. For critical realists, the outer world is there and is independent of us, and we cannot objectively prove it to be true, either by verifying or by falsifying it. So, instead of aiming to seek absolute knowledge, the expectation is that knowledge claims will offer a better interpretation of reality. Since knowledge claims are fallible, they can only contribute to improving our interpretation of reality, rather than seeking a definitive, finished truth (Cruickshank, 2003).

Critical realists do not accept positivistic views, where correlations between variables are to be taken as causal relations. On the contrary, for critical realists correlations between variables are contingent effects of underlying causal processes. Neither do critical realists accept the claims of social constructionists, who claim that all knowledge is fully contrasted. For critical realists, the production of knowledge is socially mediated but not socially determined, and science should be understood as an ongoing process in which scientists improve the concepts they use to understand the mechanisms they study.

Critical realism has been the epistemological approach used to explain how PGx is used in clinical practice, because the underpinning science and technology are out there, but the use of PGx in the clinic depends on the perceptions of different social groups (companies, clinicians, researchers, regulators, policy makers and patient groups) and how they position themselves in regards to the technology and how their position influences others. Therefore, the final use of PGx in clinical practice will depend on how the different groups involved in drug development and service delivery align their positions and define certain technological trajectories that will facilitate the use of PGx in clinical practice.

4.4 Trans-disciplinarity and policy-makers dilemmas

The aim of this thesis is not only to investigate the causes of the non-adoption of TPMT and EGFR testing, but also to extract some more general policy implications applicable across PGx disciplines, from the position of a universal and publicly funded health service such as

the NHS in the UK or the National Health Service (Sistema Nacional de Salud) in Spain. These policy implications would depend on how, the different actors in the socio-technical system in which PGx is embedded align and articulate opinions on the use of PGx, TPMT and EGFR testing.

The Policy Matrix (see Figure 4.2) will help us to uncover the policy implications of PGx that underlie the existing uncertainties and controversies that hamper the widespread use of PGx in clinical practice. This Policy Matrix (Loveridge, 2008), which, to the knowledge of the author has not been used previous for a policy analysis of PGx, illustrates the complexity of the policy-making process.

As the figure shows, there are three axes that define the policy matrix: the situation of complexity (in this case the diffusion and use of PGx in the clinical setting), the dilemmas policy makers face and their beliefs about their ability to control that situation of complexity and, the identifiable policy instruments according to the degree of control of the situation. The three elements are considered in the analysis, although the introduction of PGx will be defined in the matrix by the degree of complexity. According to this situation of complexity, policy instruments fall under three categories:

- Those under the complete control of the policy makers and their agents.
- Those over which some control can be exercised, but not complete control, and for which unexpected events and outcomes are likely to occur.
- The third group, over which control cannot be exercised and unexpected events and outcomes, will be inevitable.

So, the policy dilemmas policy-makers face, vary in complexity and, depending on this complexity, specific policies and policy instruments are implemented. For the purpose of this thesis, the Policy Matrix will be used to identify some of the policy issues that arise from the study of PGx in the context of drug development and service delivery, for which we assume that:

- PGx is highly complex and coping with its different STEEPV factors is difficult even for experts. For this reason, we would place the policy analysis on the layer "difficult even for experts".

- Due to this situation of complexity and the numerous actors that are involved in drug development and service delivery, policy-makers have only partial control over PGx service delivery.

This policy matrix will serve as a tool to understand the dilemmas that arise from the implementation of PGx and personalised medicine, and to derive some policy recommendations for implementing PGx in a public health service.

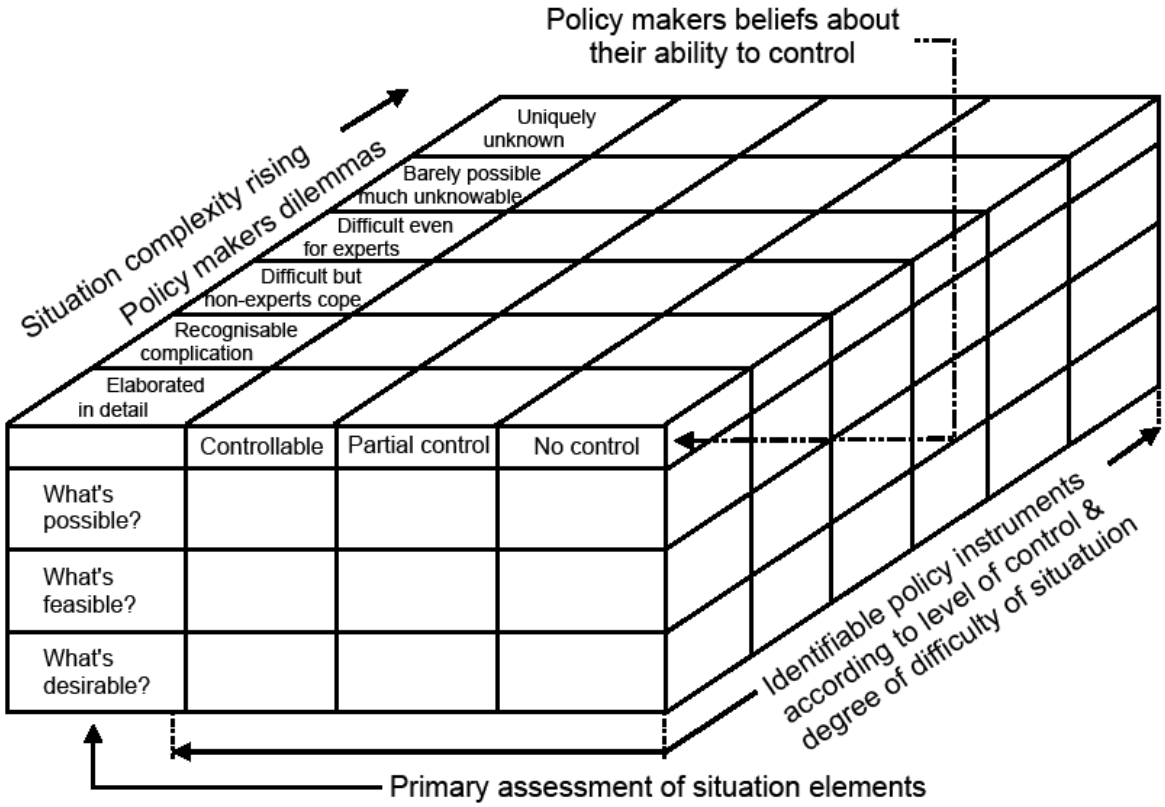

Figure 4.2.: Policy Matrix (Loveridge, 2008)

4.5 Methodology: Research design and Justification

The selection of methods was such that it would enable the gathering of arguments and opinions for and against the use of pharmacogenetics. These would give information about the benefits and drawbacks of using PGx into health service delivery.

In order to find the adequate methods, we have relied on McNeill and Chapman's (1985) four-cornered relationship between: the topic of research, the theories that underpin the investigation in the particular research topic, the research methods used to tackle the research questions and, the practical considerations that the researcher may encounter and may facilitate or hamper the research strategy (see figure 4.3).

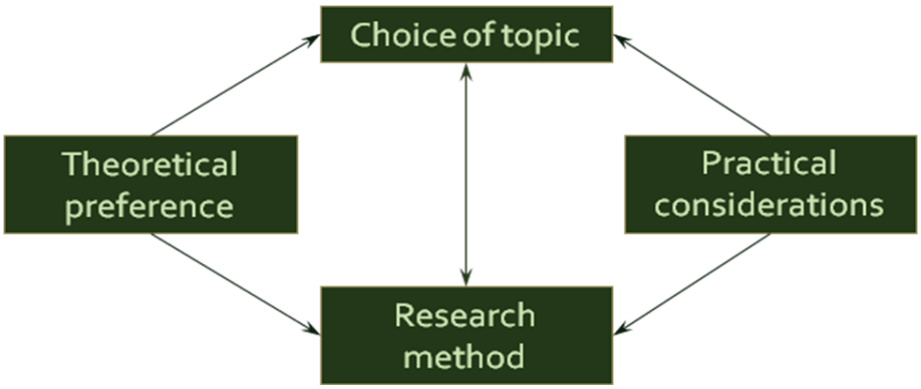

Figure 4.3: Research design model proposed by McNeill and Chapmann (1985)

Translating these four elements to our particular case, the result is the following. In order to study the diffusion of PGx innovations through a systemic approach, we consider that PGx emerges in a socio-technical system formed by actors, whose positions in regards to the technology are under scrutiny. It is here, where particular qualitative methods are used. The research is, therefore, qualitative.

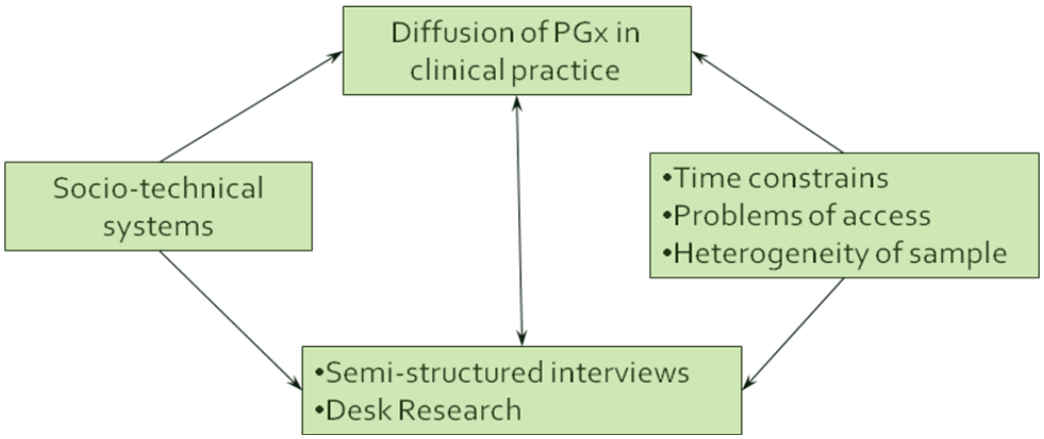

Figure 4.4: Adaptation of the McNeill and Chapmann model (1985) to the study of PGx diffusion and adoption.

4.6 Qualitative *versus* Quantitative Debate

Social research is often divided in quantitative and qualitative, or a mixture between the two. Quantitative and qualitative have often been combined, to build up a fuller and more comprehensive picture of social life. Multiple methods are used to cross-check and verify the reliability of a particular research tool and the validity of the data collected (i.e. observation data might be verified by using follow-up interviews with those being observed to confirm the validity of the researcher's observations). But, even in this case, one research method is always more represented, at the expense of the others. Here we would provide some reasoning as why we used qualitative in favor of quantitative methods.

One of the main differences between quantitative and qualitative research lies in degree of flexibility in which the research can be undertaken. While quantitative research imposes a structure on that which is being researched, qualitative research allows the structure to emerge from the data as it is collected. A survey, for example, can collect information about the questions that are included in the questionnaire but not beyond, whereas an ethnographic study, on the contrary, enables the researcher to be more involved and more flexible in terms of data gathering. One of the consequences of this is that qualitative research cannot be reproduced as happens with a piece of quantitative research (i.e. a survey that contains a fixed set of questions) (McNeill and Chapman, 1985).

In terms of the size of the samples, quantitative research deals with bigger samples than qualitative research. Quantitative research is intended to gather big amounts of information, although this is restricted to the fixed questions contained in questionnaires;

qualitative research, on the other hand, focuses on the depth of the information obtained and this does not necessarily require dealing with a big sample. In qualitative research, the size of the sample is always dependent in the size of the research group and, an alone researcher can only become involved with a relative small group of people. However, although the qualitative sample is smaller than the quantitative, this does not mean that qualitative research is easier to carry out. In fact, quantitative research is often quicker to complete, because, once a questionnaire has been finalised, the data collection and statistics can proceed very quickly with the help of a computer. The collection of qualitative data is a more lengthy process that needs to be done exclusively by the researcher (i.e. interviews), before any information can be analysed. This process usually takes longer.

4.6.1 Validity and reliability Issues

For the purpose of comparison of quantitative and qualitative methods, we would focus on three parameters: the degree of reliability, its representativeness and the validity of each method.

- Reliability refers to the use of the same method without variation in the results. Some methods are regarded as being more reliable than others and, in this case, a method that uses a alone researcher in a situation that cannot be reproduced, is at danger of not being considered reliable enough. In this sense, quantitative methods are more reliable than qualitative.
- Validity refers to the problem of whether the data collected is a true picture of what is being studied, or whether what it is said is a real representation of what it claims to be. In terms of validity, qualitative methods are stronger as they enable a more in-depth analysis.
- Representativeness refers to whether we can generalise from the sample we have taken. Quantitative methods deal with data that is highly represented, where as qualitative methods lack some representativeness because of the limitations of the sample size.

One of the main differences between quantitative and qualitative research lie in the fact that, while the quantitative researcher may claim reliability and representativeness, the qualitative researcher may claim validity. Therefore, while reliability and representativeness play in favor of quantitative research, validity plays in favor of qualitative research.

4.7 Setting the Research Strategy

Some of the PGx literature claims that PGx applies on a single case basis. For example, genetic mutations on the HER2 gene influence the response to Herceptin® (trastuzumab) in breast cancer patients. Similarly, there are PGx associations between the ALOX5 promoter genotype and the response to anti-asthma treatments. Again, the response to the anti-schizophrenia drug clozapine can be modulated by detecting mutations on the HLADQB1 gene and, response to the anti- HIV/Aids abacavir can be improved through HLA-B*5701 testing. However, the ways each of these PGx applications are currently used in clinical practice; do not respond to a systematic pattern that can be generalised across all PGx applications, for this, the thesis will look at particular case studies: TPMT and EGFR testing. The reasons for this lie in the following:

- There are a whole range of drivers that may make the pharmaceutical industry move away from the mass-production of drugs on the assumption that everyone responds in the same way, towards investing in PGx and/or personalised medicine to discover better drugs, improve the safety and efficacy of drugs under development and improve the safety or efficacy of licensed drugs (Webster et al., 2004), but the way in which it would occur is unpredictable and not generalisable.
- PGx might involve a shift in the existing interactions between drug companies. The co-development of drugs and tests sometimes might require collaborations between biotechnology and pharmaceutical companies and other times it may be a single company who co-develops a drug with a diagnostic test. The strategies of the firms involved in PGx and/or personalised therapies, are unpredictable and also vary among cases.
- The approval of PGx and/or personalised medicine drugs, such as the case of Herceptin® in the UK (for breast cancer), has proved to have been susceptible to a high degree of political influence, and this, again, is difficult to predict (Hedgecoe, 2004).
- The discovery of a molecular biomarker with a potential application in PGx and/or personalised therapy does not always assure its translation into a clinical application. For example, a series of biomarkers shown to be related to the response to the anticoagulant drug warfarin, have been identified for a number of years but they are not clinically used as predictors of drug response (Pirmohamed,

2006). This is due to the slow process of diffusion, which often depends on proved clinical evidence but also on contingent factors difficult to predict.

The implications of such a different array of factors influencing on how PGx is adopted and the difficulty of generalising these factors across all PGx applications, leads to the necessity of narrowing the research to specific case studies.

In Europe, although drugs being granted market approval by the European Medicines Regulatory Agency (EMEA), the drug regulatory agencies of every recipient country apply their own legislations and this affects the use of drugs and the use of pharmacodiagnostics in particular national contexts (see Figures 3.4 & 3.5). The reason for this is explained by the fact that:

- The structure and functioning of health care systems varies among countries, in terms of how they are organised, regulated and how they operate. Also some regulations apply in a national context and this influences how health care is delivered.
- The clinical profession gathers around networks of professionals that operate at a national level. Similarly, patient interests are represented by particular lobbying groups that respond to decisions taken in a national context.
- The fact that health care and clinical practice are framed under an institutional context that decides which drugs, diagnostic tests, other medical technologies and associated services should be approved, delivered and reimbursed, influences the way in which PGx is used in clinical practice. This explains why the diffusion of PGx cannot occur in the same fashion and through the same mechanisms across countries and why we used a comparative case study to look at how PGx is used in the UK and Spain.

The final objective of the case studies is not to give general answers, but to understand how the diffusion of PGx occurs in specific situations and to analyse common issues that emerge from the cases so that they can be extended to a higher level of policy analysis.

4.8 Qualitative data

The research methods used in this thesis are qualitative, which have been produced by document analysis, observations and interviews. Qualitative research tends to be based on the intensive study of a relative a small number of cases, although this raises questions on how representative those cases are.

In order to avoid issues about representativeness of the cases, we started the research by an exhaustive literature review where we looked at the existing literature on pharmacogenetics, in order to identify gaps that haven't been explored before or issues that may contribute to the existing work already done.

4.8.1 Document Analysis

The desk research was aimed at exploring the radical nature of PGx, as well as exploring the case studies more in depth. It took two forms. In first place, we did an exploratory search where we aimed to gather technical information about PGx technologies and associated clinical practices, as well as information about the socio-economic environment that affected these. The sources of evidence consulted were: biological and medical journal articles; socio-economic studies also published in journal articles as well as other reports; product brochures; newspaper articles and some unpublished work.

The desk research was also intended to look for secondary data that could support the information obtained in the interviews. This secondary data was found, mainly in government publications; regulations; clinical trial protocols; patents.

All these documents provided empirical data that gave information about the current state of the specific cases the thesis deals with, as well as the existing controversies and ongoing debates around them.

4.8.2 Semi-Structured Interviews

The people interviewed were clustered into groups of expert researchers (geneticists, biochemists, pharmacologists, medical researchers, health economists and sociologists); clinicians (haematologists, oncologists, gastroenterologists and rheumatologists); personnel from pharmaceutical and biotechnology companies; regulators and patient groups.

The objective of the interviews was twofold:

- First, it aimed to get the views and opinions of experts in PGx and analyse their position in the ongoing PGx debates.
- Second, it looked to accelerate the learning process through which it is possible to visualise possible options for PGx and personalised forms of health service delivery.

The use of semi-structured interviews with open-ended questions facilitated flexibility during the interview process and, in opposition to rigid structured interviews, enabled the exploration of particular issues specific interviewees may be familiar with.

The interviews were conducted at times and places convenient for the interviewee. The majority of the interviews were face-to-face and took place at their place of work, although if a face-to-face interview was not possible, then a telephone interview was conducted.

The interviewees were asked to give verbal consent with regards to the recording of the conversation. The majority agreed although some preferred not to be recorded. In such cases, notes were taken. The same procedure applied to the telephone interviews.

Interviews were transcribed manually and analysed afterwards, without the use of any software. Reading the whole interview during the analysis gave a better insight into the issues discussed.

A total of thirty-seven interviews were undertaken, twenty-nine in the UK and eight in Spain (see section 4.8.2.3).

In principle, five different batches of questions were tailored to each of the expert groups: researchers, clinicians, pharmaceutical and biotechnology companies' personnel, patient groups and regulators. These questions were intended to be a guide during the interview process and not a rigid script to follow as the interviews also had to allow unexpected themes to be explored.

4.8.2.1 Sources of Expert Opinion

The interview questions needed to address current PGx issues about technology, sociology, economy, ethics and politics around TPMT and EGFR testing. For this, it was important that these were directed to experts in the field. However, finding an expert is not an easy task. When giving an opinion, an expert (unlike a non-expert) manipulates and integrates the

knowledge from all the six elements of the STEEPV acronym (Social, Technological, Economic, Ecologic, Political and Values), for this reason, the people addressed in the interviews needed to be carefully selected.

During the experts search, we relied on two search sources. In first place, we selected experts from the literature, we invited them for an interview and, once they accepted, we asked them to suggest other experts in the field. This process, like snowball sampling, aimed to search for recognised people among a particular community. In health research this is also known as "snowball" sampling, or the method that helps in identifying key informants and people with particular knowledge, skills or characteristics and has proved effective in health research (Streeton et al., 2004).

Therefore, the purpose of the interviews was finding key informants that could provide reliable opinion about the benefits and hurdles of introducing TPMT and EGFR testing in clinical practice, as well as dealing with more general questions about PGx. But, since not every individual involved in TPMT and EGFR testing is an expert in each of these areas (a clinical researcher has different professional aims to those of a regulator or a policy-maker), we appointed specific individuals who, at the same time as being familiar with either TPMT or EGFR testing, they would give specific responses and **opinions according to their specific field of expertise**. For this, w**e addressed clinicians, regulators, policy-makers and patient associations**.

4.8.2.2 Population of experts and their distribution

A total of thirty-seven interviews were undertaken, twenty-nine in the UK and eight in Spain. The distribution of the interviews was as follows:

- In the UK, fourteen researchers were interviewed, six members of pharmaceutical and biotechnology companies, seven clinicians and two members of regulatory agencies.
- In Spain, the distribution was as follows: three researchers, three members of pharmaceutical and diagnostic companies and two clinicians.

The mini-questionnaire on the EGFR case was distributed among eighteen clinicians, from which nine responded.

4.8.2.3 Distribution by clinical discipline

In terms of clinical discipline, from the twenty nine interviews done for the TPMT and EGFR UK cases, the distribution was as follows for the UK cases:

- From the fourteen researchers interviewed in the UK, seven where life science researchers, all of them involved in TPMT testing, doing research only or research and service provision (in the case of the reference laboratories contacted). The other seven were social science researchers. From these, three of them had done previous work on TPMT testing. The four remaining were experts in PGx although not in TPMT testing specifically.
- From the six interviewees with a company affiliation, five were involved in either drug or test development for Non-Small-Cell Lung Cancer (NSCLC). One of them was involved in other commercial PGx applications for breast cancer. No commercial company participated in the TPMT case in the UK.
- In terms of clinicians, we interviewed seven: four for the TPMT case (a rheumatologist, two haematologists and a gastroenterologist). No dermatologist agreed to be interviewed, although, TPMT testing was already common practice in dermatology so no anticipated controversies were envisaged.
- Finally, two respondents had a regulatory affiliation. They were involved in regulating pharmaceuticals and, although they had extensive knowledge about PGx, they were not directly involved in any of the cases.
- We also got responses from two patient organisations contacted, although they did not agree to do a full interview since they considered PGx was not relevant for them. Five other patient organisations did not responded to our queries for interview.

For the Spanish case we did eight interviews, all in relation to the TPMT case. The distribution of the interviews was as follows: three researchers, two clinicians (gastroenterologists) and, in contrast with the TPMT UK case where no companies were involved, three persons with a company affiliation.

Distribution of interview EXPERTS by COUNTRY and by EXPERTISE					
COUNTRY	**Company**	**Regulatory Agencies**	**Clinicians**	**Researchers**	**Patient Groups**
UK	**6** *5 EGFR related, 1 breast cancer related-no TPMT*	**2**	**7** *4 TPMT related, 3 EGFR related*	**14** *7 science researchers and 7 social science researchers, all TPMT*	**0**
Spain	**3** *All TPMT related*	*Same as above*	**2** *All TPMT related*	**3** *All TPMT related*	**0**
Total	**9**	**2**	**9**	**17**	**0**

4.8.2.4 Geographical boundaries

The smaller number of interviewees in Spain was justified by the fact that the Spanish case aimed to explore how different institutional settings affect the adoption of PGx, complementing the results obtained in the UK. However, the main research burden lies in the diffusion of PGx in the UK, for this, the majority of the interviews took place in the UK.

In regards to EGFR testing, we did not carry out a comparative study because, EGFR testing is not yet used in the clinic (it is only a research tool), neither in the UK nor in Spain. For this reason, we considered that the institutional comparison was not relevant for this case.

4.8.3 Case Studies

The case study approach is used when the researcher investigates a situation in-depth, in particular, looking at the processes and relationships within a setting. Case studies are used, predominantly, to the discovery of information and, less commonly to test theory (Denscombe, 2007). They are, however, the best way of combining theory with empirical data (Zartman, 2005)

Case studies are a particularly justified strategy to study particular phenomena in a real-time context, analysing operational links over time, rather than frequencies that might be obtained through quantitative data. They are often suitable to answer questions of "how", "why", "who", "what", "when" and "where" and can be exploratory, explanatory or descriptive.

Case studies require direct observation of the event being studied as well as interviews with the persons involved in the events, although other sources of evidence such as document analysis are also considered. **One of the strengths of case studies is their capacity to deal with a broad range of sources, providing a broad view of the real-life events under scrutiny. One of the weaknesses of case studies is that they provide little evidence for scientific generalisation.**

Case studies are selected on the basis of known attributes, which need to be made explicit and justifiable. However, the case study approach requires that the researcher makes choices from a number of possible events, people, organisations and the like (Denscombe, 2007). In case study research, the researcher needs to pick up one example or just a few, from a wider range of examples, not seeking a statistical generalisation but looking for the subtleties of complex social situations. The case study also aims to make some generalisations, although these should be done acknowledging the strengths and limitations of the method. Case studies are unique, although they can also give an idea of the broader state of things. Also, the extent to which the results of the case study can be generalised depends on how similar is this case to other cases (Denscombe, 2007).

For the purpose of generalisation, the use of case studies aims to identify critical points and contested elements that currently hamper the widespread use of these tests and which are generalisable to other tests. These can only be identified by looking at the opinions that experts in the field have. These experts would also give ideas on how to improve the access to these tests (and therefore to PGx) through a public health system like the NHS.

The thesis involves two case studies: TPMT and EGFR testing, with a country comparison (UK-Spain) for the TPMT case.

4.8.4 Comparative Case Studies

Single case studies are of inherently limited utility in producing knowledge. In contrast, comparative cases exhibit the advantages of in-depth analysis of reality while overcoming the weaknesses of focusing on one case. Therefore, multiple cases allow the analyst to develop a deeper understanding of the details of the case, so that the data can be fully explored, explained, and understood.

The simplest way to achieve comparison is to examine multiple variables in the same case. For example, instances of failure can be compared with instances of success in the same

country in a comparative analysis that uses specific concepts. In this thesis, we analyse in depth multiple variables within the case of TPMT testing, introducing a country comparison between the UK and Spain.

On the other hand and, as it occurred with the second case (EGFR testing), if multiple instances within a single case are not available, then similar cases cannot be compared.

4.8.4.1 Country Comparison

The intention of a TPMT comparison between Spain and the UK, responds to the fact that TPMT was one of the first PGx biomarkers discovered and one of the first diagnostic tests developed and implemented in clinical practice in both countries. This provides a ground for analysis on how PGx is being used in service delivery, TPMT is an "older" PGx test than EGFR and there are already some studies that have analysed its socio-economic implications in four European countries: Germany, Ireland, the Netherlands and the UK. Therefore, while the UK TPMT case aims to contribute to the existing literature, the TPMT comparison between the UK and Spain aims to add something new to the existing literature, by analysing how the institutional settings in the UK and Spain may affect PGx service delivery. At this point we considered that, for the purpose of analysing the institutional context of both countries and how these affected PGx, it was enough to restrict the analysis to the TPMT case only, in particular, taking into account that EGFR testing was a diagnostic test for research use only.

4.8.4.2 Non-comparable cases

The differences among the TPMT-EGFR cases enable to examine two very different PGx applications, where we will try to extract common issues that could be extrapolated to a higher level of policy analysis. However, both cases cannot be compared directly because, while the main issue in the TPMT case is whether TPMT testing could improve the prescription of AZA and 6-MP (both drugs have been in the market for decades); in the case of EGFR testing, the main issue lies in the use of two new drugs (Iressa® and Tarceva®) and afterwards, in how EGFR testing could improve the use of these two drugs. So, while in the first case, the major uncertainty is whether TPMT testing will be widely used to prevent ADRs associated with AZA and 6-MP, in the second, the major uncertainty lies in the use of Iressa® and Tarceva® and the indications these drugs will be approved for. In this case study, the use of EGFR testing helps building a discussion of how the test may influence the

future use of Iressa® and Tarceva® because, at present (and unlike with TPMT testing), EGFR tests are not used in clinical practice and only for research purposes. Therefore, there is a time lag between both case studies, with TPMT testing being clinically used earlier on in time than EGFR testing. More details about the differences and similarities among cases are given in section 1.9 EGFR and TPMT Testing.

4.9 Limitations and Appropriateness

4.9.1 Gaining Access

Gaining access to groups of respondents whom you wish to interview or distribute a questionnaire to can pose serious practical problems. The researcher needs to know how accessible the target population is and how literate it is with the research that is being carried out.

Once the potential interviewees had been identified, they were contacted by e-mail, to ask if they would be prepared to take part in an interview. The e-mail included information about the research project, the potential role of the interviewees in the research project and an invitation to attend an interview. If potential respondents did not respond in the first instance, they would receive a second e-mail. When an individual agreed to take part in the interview, arrangements were made for the interview to be conducted.

If interviews could not take place face-to-face, they would be undertaken over the telephone.

The purpose of this mini-questionnaire (see annex) was not to obtain statistical results but, in contrast, to obtain information about issues that would have been discussed during the interviews, if these had taken place. In total, the mini-questionnaire (see annex) was sent to fifteen clinical oncologists, of which eight replied.

4.9.2 Ethical Considerations

This research has been granted academic approval by Manchester Business School and ethical approval by the Research Ethics Committee of the University of Manchester (REF: TPCS/CA/*ethics*/07273). Following the granting of ethical approval by the University, insurance policies were put in place by the Research Office of the University of Manchester to cover both the sponsorship of the research and the research activities associated with the

thesis. Access to interviewees working in or for the NHS also required ethical as well as R&D approval. Ethical approval was granted by the South West Research Ethics Committee (REF. 084/H0206/5) and R&D approval was granted by the R&D departments of the four hospitals involved in the research.

As the research was carried out in different hospitals, each of them required specific information for their sites. All the hospital R&D departments were provided with the research proposal, research protocol, the Research Ethics applicant's checklist, as well as the letters of approval from both the University and the Research Ethics Committee. Some hospitals also required specific documents for their sites: a research passport to enter their premises, a confidentiality agreement to ensure that the interviews were done under confidentiality and an Honorary Research Contract for the period of the research.

4.9.3 Problems of Access

The search for potential respondents faced three main hurdles:

- Gaining access to NHS employees was restricted to e-mails, so if a potential respondent did not reply to the e-mail, no further telephone call could be made. According to the research protocol submitted to the South West National Research Ethics Committee (REF. 08/H0206/5), no interviewee from the NHS would be contacted by other means than e-mail and not more than twice, this restricted the access to some clinicians.
- The access to patient associations was not successful and these groups were not represented in the interviews. Six patient groups were contacted but they either did not reply or declined to attend an interview. Two of them gave a brief explanation about their research projects via e-mail. In order to circumvent this hurdle, some data analysis referring to patient groups was obtained.
- The Spanish case study aimed to interview gastroenterologists, as this was the clinical specialty for which TPMT was used. However, some of the clinicians contacted said they did not have enough understanding about TPMT testing. For this reason, only two clinicians could finally be interviewed in Spain.

4.9.4 Resolving Problems of Access

The difficulty of gaining access to some of the clinicians during the first set of interviews (in the TPMT case) was taken into account during the second set of interviews. Besides doing some face-to-face interviews, and in order to overcome time constraints, some clinical oncologists from a hospital were sent a very short questionnaire targeted at obtaining yes/no answers to some of the key issues around EGFR testing. These clinicians were first approached in an e-mail, where the nature of the research was explained. A second e-mail would have the questionnaire attached. Clinicians did not need to provide their names in order to maintain their confidentiality and they could send the questionnaires back either by e-mail or by post.

4.10 Summary

In conclusion, this chapter sets out the theoretical and methodological approach to the research. If, in previous chapters we identified the object of our study (the problem of the non-adoption of PGx in the clinic), in this chapter we define the socio-technical system in which the problem is framed. This system is formed by actors involved in drug development and service delivery, whose interactions affect the way in which PGx is likely to evolve. By targeting these actors, we aim to gather their opinions and understand the current uncertainties and controversies that underpin the non-adoption of the technology. The purpose of the interviews is gathering the opinion of these actors (researchers, clinicians, regulators and policy-makers, pharmaceutical and biotechnology companies and patient groups), and envisage possible options for service delivery. Finally, and in order to have a fully-fledged understanding of the problem, we tailored specific research protocols for each of the interviewees, which we complemented with extensive document analysis.

Chapter 5. TPMT Testing in Autoimmune Diseases and Acute Lymphoblastic Leukaemia in the UK

The aim of this chapter is to illustrate the current use of TPMT testing in the treatment of autoimmune diseases and acute lymphoblastic leukaemia. The chapter describes the controversial nature of TPMT testing and the implications that these controversies have on future service delivery mechanisms. It analyses the socio-economic and technological actors that currently drive the use of TPMT testing in the clinic. The chapter begins with an introduction to the drugs used to treat autoimmune diseases and acute lymphoblastic leukaemia (azathioprine AZA and 6-mercaptopurine 6-MP). It goes on to look at the adverse drug reactions (ADRs) caused by these drugs, the management of these ADRs through TPMT testing, the implications of TPMT testing for current service delivery mechanisms and regulatory frameworks, and finishes by identifying some gaps that hamper the widespread use of TPMT testing in clinical practice.

5.1 Thiopurines

The drugs 6-MP and AZA belong to a family of drugs called thiopurines. Thiopurines are widely used immunosuppressant therapies (they target the cells of the immune system) and their mechanism of action consists of the blockage of cell duplication, by inhibiting the replication of the DNA. When 6-MP or AZA are metabolised by the organism, they are converted into 6-thioguanin nucleotides or 6-TGNs, whose structure is very similar to that of the nucleotides of the DNA and can easily be "confused" with them. When this happens and a TGN is inserted "by mistake" into the DNA, it blocks the mechanisms that are necessary for DNA replication and as a result the cell cycle stops (see Figure 5.4).

The structures of 6-MP and AZA are very similar. 6-MP is a pro-drug that is transformed in the liver into AZA, without the action of any enzyme (see Figure 5.1). Structurally, the molecules are similar, but clinically 6-MP is used to treat acute lymphoblastic leukaemia (ALL) and AZA is used after organ transplant surgery and for autoimmune diseases across

different clinical specialities: AZA is used to treat dermatologic disease, rheumatoid arthritis, lupus erythematosus, autoimmune hepatitis and renal and cardiac transplantation (Coulthard and Hogarth, 2005, Weinshilboum, 2001).

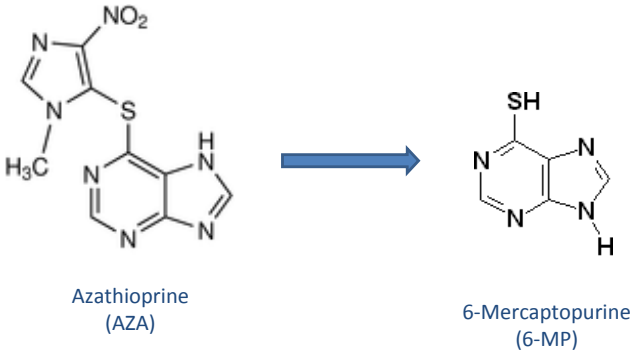

Figure 5.1: Molecular structure of AZA and 6-MP

AZA is commercialised under different branded names in different countries (Imuran®, Imurel®, Azasan®) and 6-MP is commercialised under the name of Purinethol®. AZA and 6-MP patents were granted in the late 1950s to Burroughs Wellcome (later Wellcome, Glaxo-Wellcome and now GSK). The first AZA US patent expired in 1979 and, soon after, the remaining patents in other countries followed, leading to commercial drugs being open to competition from generics.

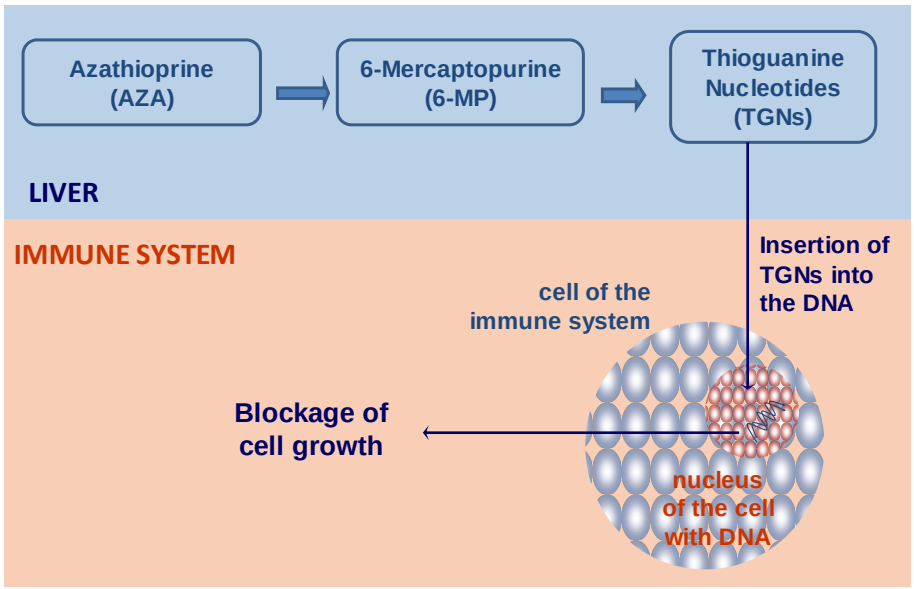

Figure 5.2: Schematic representation of the mechanism of action of AZA and 6-MP

Even though both AZA and 6-MP are widely used immunosuppressant drugs, they have a relatively low therapeutic index (Weinshilboum, 2001). This means that the difference between administering a drug dose that enables a patient to reach an optimal response and one that would lead to the patient experiencing an ADR is not very wide. Nevertheless, as happens with any other drug, ADRs occur at different degrees of severity. The most serious ones often lead to patient hospitalisation and in some cases can be fatal.

The metabolism of AZA and 6-MP involves the action of various enzymes (see Figure 5.3), although for the purpose of this thesis we will focus on just two of them: Xantine Oxidase (XO) that transforms 6-MP into oxidised metabolites, and Thiopurine Methyl Transferase (TPMT) that transforms 6-MP into another chemical component (6-Methyl Mercaptopurine).

5.2 Adverse Drug Reactions

AZA and 6-MP, like any other drug, cause some ADRs (Loon and Weinshilboum, 1987). The most common side effect caused by 6-MP and AZA (in more than 10% of cases taking 6-MP) is myelosuppression, or a reduction in the ability of the bone marrow to produce blood cells (platelets, red blood cells and white blood cells) that makes patients susceptible to a higher risk of infection, bleeding or anaemia. The most common type of myelosuppression associated with AZA and 6-MP is a type of leucopenia (low levels of white blood cells in the bloodstream) known as neutropenia (Weinshilboum and Sladek, 1980). Neutropenia affects the neutrophil granulocytes, specific white blood cells that are the primary defence against bacteria in the blood. Patients with neutropenia are very susceptible to infections and, without accurate treatment, can be at risk of death.

Another serious side effect associated with AZA and 6-MP is hepatotoxicity (between 1 and 10% of the patients treated with the drugs suffer from it) and hepatic injury. Also, severe liver damage can occur with any dosage, but seems to be prevalent when standard doses are exceeded (>2.5 mg/kg/day) (GlaxoSmithKline, 2002).

The manifestation of ADRs in any patient taking AZA or 6-MP is triggered by the accumulation of TGNs in the blood, therefore, measurements of TGNs in the blood can be taken as an indication of drug efficacy and toxicity (Lennard and Maddocks, 1983). But other variables can also influence adverse events and can be used as indicators of drug response. These factors are: polymorphisms (or mutations) in the Thiopurine

Methyltransferase (TPMT) gene (Van Loon and Weinshilboum, 1982) as well as the concentration of the enzyme TPMT in the blood (Woodson and Weinshilboum, 1983).

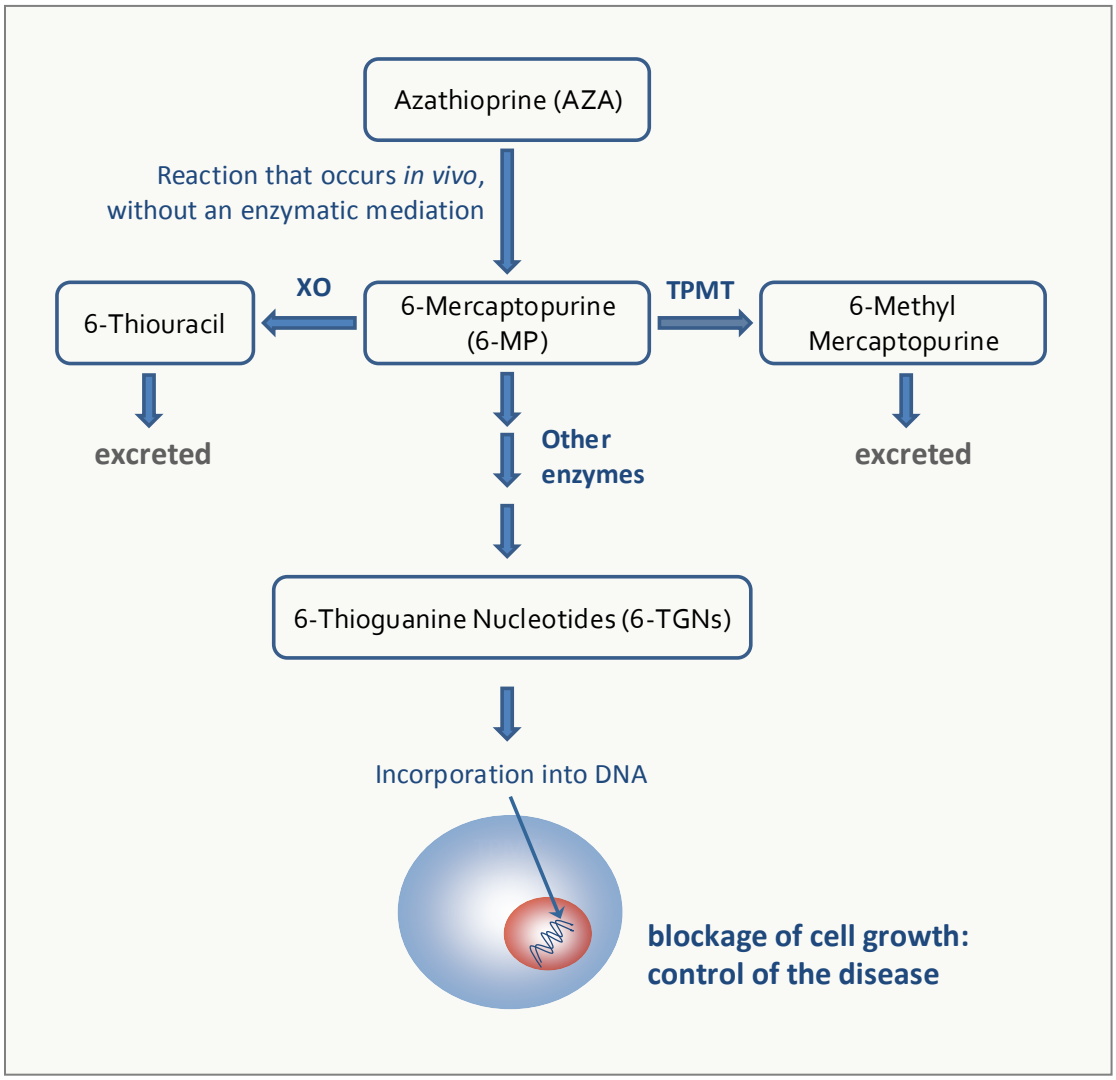

Figure 5.3: Representation of the normal metabolism of 6-MP and AZA ((Weinshilboum,

Some of the ADRs associated with 6-MP and AZA are caused by a lack of the TPMT enzyme in the liver. The alteration of the drug metabolism as a consequence of this lack of enzyme is represented in Figure 5.4 The lack of TPMT implies that 6-MP cannot be converted into 6-Methyl Mercaptopurine and, as a consequence, the whole metabolic process is displaced towards a major production of 6-thiouracil and 6-thioguanin nucleotides (6-TGNs), which are at the origin of the ADRs. The function of the 6-TGNs is to block the activity of the cells of the immune system that have lost their control and started recognising their own cells (of an individual) as "strangers", and destroying them. 6-TGNs deploy this process of "auto-destruction", but when 6-TGNs reach a higher concentration than normal (because of some physiological alterations), they become toxic and originate an adverse event in the patient

who is taking AZA or 6-MP (Lennard and Maddocks, 1983). Detecting when a patient is at risk of experiencing an ADR (myelosuppression among others) is crucial for avoiding these adverse reactions.

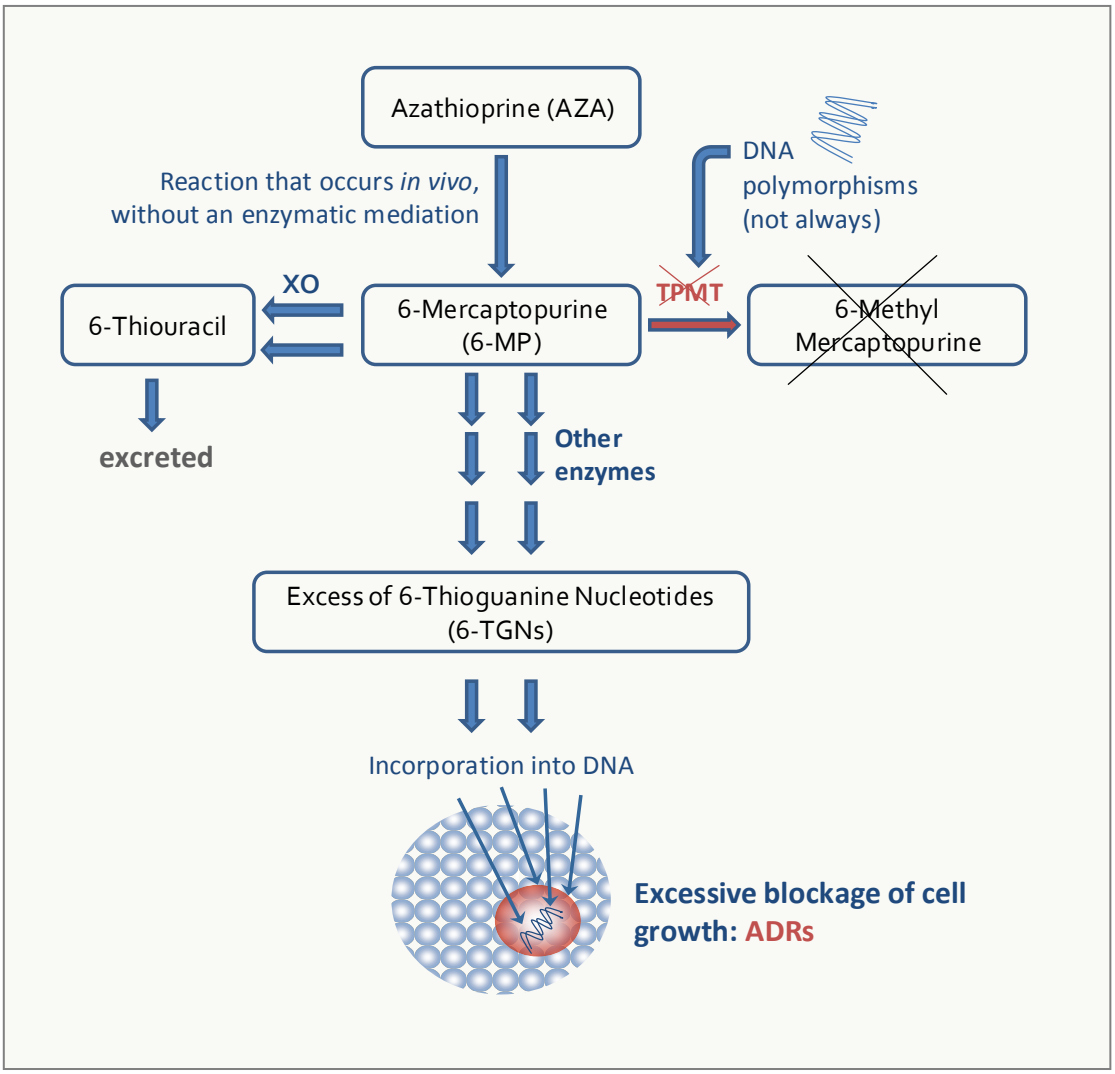

Figure 5.4: Representation of the biochemical reactions at the origin of the ADRs associated with 6-MP and AZA (Weinshilboum, 2001)

Traditionally, drug monitoring has been done after a patient has started a treatment with AZA or 6-MP, by measuring the levels of thioguanine nucleotides (TGNs) in the blood. TGNs are a product of the metabolism of the drugs and when they are too high, this is an indication that the patient is likely to develop a myelosuppression (Evans et al., 2001b), in which case the treatment should be interrupted or the dose should be adjusted. However, despite the measures on the levels of TGNs (also accompanied by blood cell counts) that aimed to prevent ADRs, sometimes patients had already developed serious adverse events

because theyr extreme sensibility to the drugs. In these cases, predictive testing would avoid some of these ADRs.

Since variations in the concentrations of TPMT, as well as TPMT polymorphisms, influence drug response, it is possible to develop mechanisms through which ADRs can be predicted. This is the promise of PGx and personalised medicine: improved drug prescription through diagnostics testing, either genetic or phenotypic, either by measuring the levels of the enzyme TPMT in the blood (through phenotyping) or polymorphisms on the TPMT gene (genotyping).

5.3 TPMT Phenotyping

Phenotyping is a TPMT testing and consists of measuring the level of the TPMT enzyme. TPMT is a liver enzyme although it is also present in the blood, therefore sampling is relatively easy. The availability of the sample makes it an easily provided service (Holme et al., 2002).

TPMT testing can be done either by using radiochemical activity assays, which label the enzyme with radioactivity, or through chromatographic techniques such as High Performance Liquid Chromatography (HPLC). HPLC measures directly the concentration of enzymes in a protein sample obtained from the blood cells. Phenotyping occurs as follows:

1. Blood samples arrive at the hospital laboratory every morning (approximately 60-70/day), where they are labelled with a bar code to grant the patients anonymity.

2. The samples then pass to another room where a small volume of blood is taken for protein extraction and TPMT testing. Traditional methods only separate red blood cells. However, newer methods analyse the whole blood sample, because the processes of washing the red cells during the preparation of samples could bias the results. Therefore, white cells give more information (Ford et al., 2004a).

3. Once the "mixture" of proteins is ready for analysis, a parallel sample is taken for a haemoglobin test. Concentrations of haemoglobin are correlated with the concentration of TPMT.

However, this correlation might not always be real as anaemic patients might have a lower haemoglobin concentration but this does not necessarily mean that each cell has lower TPMT levels. The haemoglobin levels just complement the results of the TPMT test.

The next step is to analyse the samples using a radio-immunochemistry method or a chromatographic technique.

- The radio-immunochemistry method requires the use of antibodies that recognise TPMT enzymes, as well as a radioactive label that emits light once the antibodies and the enzymes are recognised.
- The chromatographic method (HPLC) directly separates TPMT enzymes from the rest of the proteins in the sample. The machine consists of a column of resin through which all the proteins pass and, according to their physical-chemical characteristics, are sorted. The technique is standardised manually so as to detect at which point (how many minutes after the injection of the protein mix into the column) TPMT is eluted (or ejected from the column). Depending on when the protein sample is sorted in the chromatographic column, we can predict if the individual has no or very low levels of TPMT in the blood; whether he/she has low levels of enzyme; or whether these levels are normal or even high. Chromatography gives a picture (or chromatogram) when the sample is sorted through the column. Figure 5.5 is a representation of the possible peaks of the elution of TPMT. The peak on the left of the graph is indicative of patients with very low levels of enzyme. The sample has a "lighter" content of TPMT and elutes better. The peak in the middle corresponds with blood samples with a low level of the TPMT enzyme and the peak on the right to patients with normal or high levels of TPMT. However, sometimes there is no peak, and this is indicative of an anomaly in the phenotyping test, which is not able to deliver the patients TPMT status. These samples go for genotyping (a very small number of the 60-70 samples that enter the laboratory) (respondents 1 & 3).

TPMT testing could then (Holme et al., 2002):

- Identify those individuals with very low or undetectable levels of TPMT who could develop a serious reaction and should not take thiopurines (6-MP or AZA).

- Identify patients with low TPMT levels who might benefit from the drug at smaller doses (although not all patients with low TPMT levels would benefit from a dose reduction), and finally,
- Identify patients with normal levels of TPMT that will have no problems responding to AZA or 6-MP.

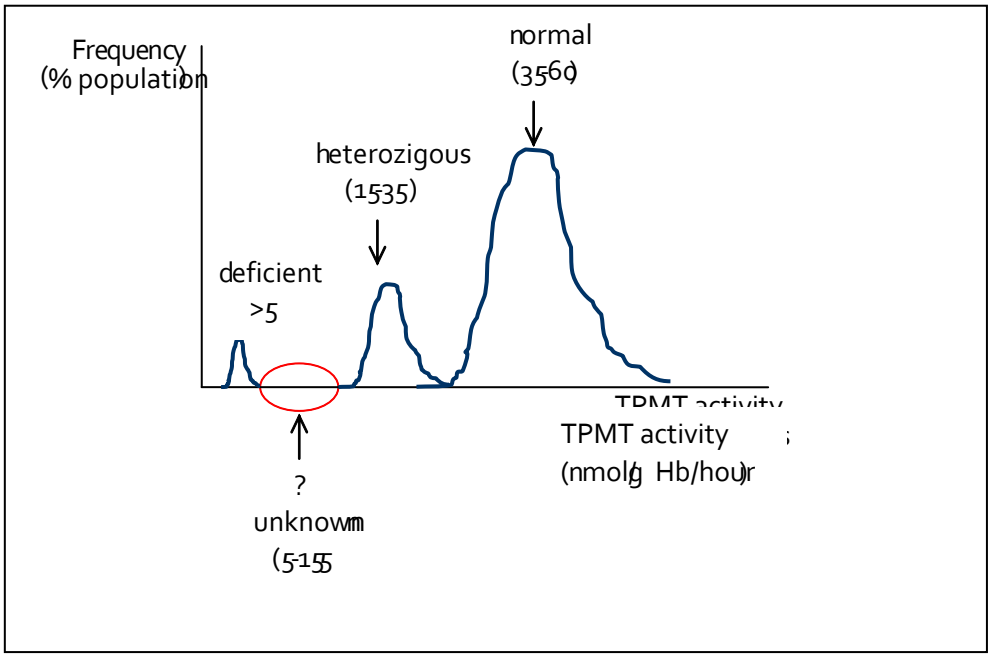

Figure 5.5: HPLC chromatogram with a representation of the peaks that identify the patients with very low or no TPMT in their blood, those with low TPMT levels and those with normal or high TPMT levels.

5.3.1 Weaknesses associated with phenotyping

Although the anticipated benefits of TPMT phenotypic testing, the analysis faces some difficulties and poses several questions, in particular concerning its validity for the drug management of patients with acute lymphoblastic leukaemia (ALL):

- Phenotyping is not possible after a blood transfusion, which is often required by leukaemia patients, because the levels of TPMT of the patient are altered by the blood which has been transfused.
- There are differences between the levels of TPMT in the blood and the levels of TPMT inside the patient's tumour. Often, because a tumour is the result of a deregulation of gene expression, the levels of TPMT inside it are altered and do not correspond with the TPMT levels in the blood. So, for example, if a patient has low

or normal TPMT levels but the tumour has high TPMT expression, s/he would metabolise thiopurines normally but the tumour would metabolise them even faster. As result, while the patient would be metabolising an adequate amount of the drug, the tumour would not receive a sufficient drug dose. In cases like this, it is not possible to establish a correlation between the levels of TPMT and drug doses and, the patient should be given an alternative treatment (respondent 24).

5.4 TPMT Genotyping

TPMT genotyping consists of looking at the TPMT gene and searching for polymorphisms (or mutations) that may be involved in drug response (see Figure 5.6). According to the genetic profile, individuals fall into one of these three categories:

- Individuals who exhibit a normal metabolism of thiopurines because they have normal (or even high) levels of TPMT and respond to the drugs without major problems. This means that these individuals have two "wild"[7] alleles or are homozygous[8] for the high TPMT alleles (TPMTH/TPMTH), H standing for high levels of TPMT.
- Individuals who have very low or undetectable levels of TPMT. It is most likely that these individuals will accumulate TGNs in the blood. The genetic profile of these individuals is (TPMTL/TPMTL), L standing for low levels of TPMT.
- Individuals with a heterozygous profile (TPMTL/TPMTH) and who have low levels of TPMT in the blood and whose adverse response to thiopurines might be due to their genetic profile, but might also be due to other factors (Arenas et al., 2006). There are indications of some association between having low levels of TPMT in the blood and having a heterozygous genetic profile for TPMT (Evans et al., 2001a), although this has not yet been demonstrated in all patients and still some of the individuals who have a heterozygous genetic profile do not show low concentrations of TPMT in the blood.

The methods used for genotyping consist of extracting DNA from a blood sample and searching for specific polymorphisms on the TPMT gene through various techniques:

[7] The term "wild" is used in genetics for genetic profiles that are not mutated or polymorphic.

[8] Definitions of the terms "alleles" and "homozygous" are in the lexicon.

Restriction Fragment Length Polymorphism (RFLPs), denaturing HPLC, Real-time RT-PCR (Polymerase Chain Reaction), arrayed primer extension (APEX) assay, molecular haplotyping or PyrosequencingTM (direct sequencing) (Coulthard and Hogarth, 2005).

5.5 The TPMT gene

TPMT is a gene situated in chromosome 6 that contains 23 known polymorphisms (or variations in the DNA) (see Figure 5.7). Each of these would have a normal, a heterozygous and a homozygous profile. But from these 23, the ones that appear most frequently among the population are polymorphisms on the alleles[9] TPMT *3A (a combination of *3B and *3C), *2 and *3C (dominant in black races and Asians).

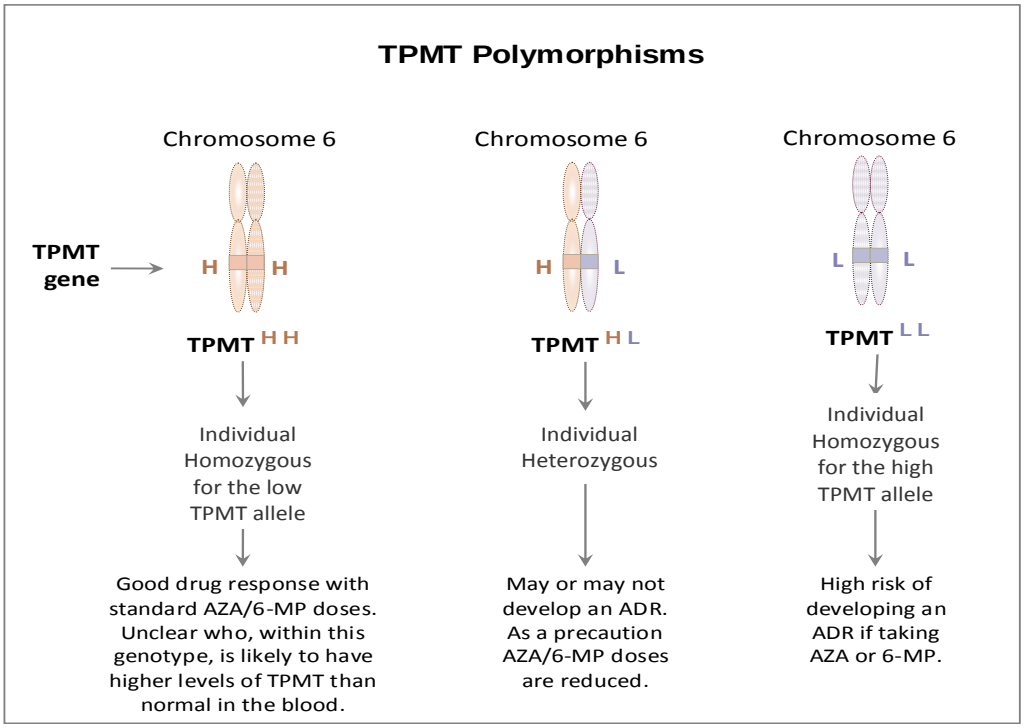

Figure 5.6: Representation of the chromosome 6 (where the TPMT gene is situated), with its allelic variants. These allelic variants can occur at different genetic points, the most common ones being: TPMT*2, *3A, *3B and *3C.

There is also evidence that mutations in other genes, such as the MTHFR (Methylenetetrahydrofolate reductase), may also affect the response to thiopurines (Arenas et al., 2005) and this may be another factor to consider for future service delivery.

[9] Alleles are used to define a specific DNA sequence or physical space inside a gene. Variations in an allele are defined as polymorphic variants of the allele or genetic polymorphisms.

Figure 5.7 represents all the known polymorphisms in the TPMT gene. It is not very clear how they each influence drug response, only which are the most common ones (*3A, *2 & *3C).

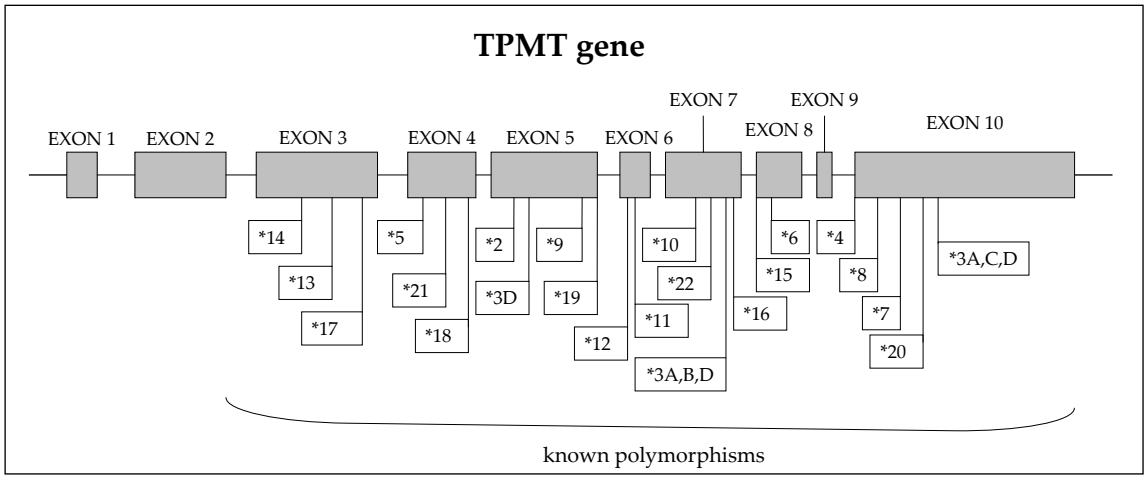

Figure 5.7: Representation of the TPMT gene, with all the regions where genetic polymorphisms may be found. Each of these regions can then have three different allelic variants: homozygous for "Low" TPMT levels, heterozygous and homozygous for "High" TMPT levels. Exons are the functional

5.6 Reference Laboratories

TPMT testing services in the UK are offered by two reference laboratories, one in London and one in Birmingham. The laboratories offer TPMT testing to any hospital in the UK. The first one, Purines Laboratory at Guy´s Hospital (London) is part of the Metabolic Diseases Group, which is also a member of the Supra-Regional Assay Service. The latter organisation was initiated in 1974 by the Department of Health (DoH), after this institution recognised the need to investigate certain conditions whose nature or frequency was best suited to be undertaken in designated centres of excellence. In this way Guy's Hospital became a reference centre for genetic enzyme testing, offering tests for enzymatic disorders as well as some complementary metabolites.

The Purines Research Laboratory is part of this enzymatic service and, focuses on the analysis of disorders related to the metabolism of purines and pirimidines, for this reason started specialising in TPMT enzyme testing in 2002. However, TPMT genetic testing remained, mainly as an investigational approach, because in the majority of cases, the benefits of phenotyping outweigh those of genotyping:

- Genotyping gives genetic information that is invariable throughout a person's life.

- Phenotyping gives information about the phenotype of the patient when the test is done. The phenotype may vary depending on environmental factors, even when the genotype remains. For this, even if a patient's genotype indicates that he will respond well to a drug, there may be other factors (e.g. interaction with other drugs) that will cause the genotype (TPMT HH) to correspond not to a person likely to demonstrate a good response but to someone who has lower TPMT levels than normal.

Nevertheless, the Purines laboratory has demonstrated an interest in the investigation of other genetic aspects associated with the metabolism of thiopurines and not only of the TPMT gene (Arenas et al., 2006, Arenas et al., 2005). It should be noted that Guy's Hospital is a university hospital linked to King's College London and some of its research projects result from collaboration between the two institutions. Gene testing in the Purines lab is only done at a research level and most of the gene testing that has been done in the past three years was part of a PhD Project.

The Clinical Biochemistry Department at Birmingham Hospital is the second reference laboratory that offers TPMT testing services. The service was set up in 2003, with some funds the laboratory had available to obtain some equipment and start analysing samples. The biochemistry department, in contrast to the Purines Research Laboratory, was not a laboratory specialising in metabolic conditions, but a biochemistry department offering routine blood monitoring for the hospital. The Birmingham laboratory, in contrast with the London laboratory, needed to set up a completely new service: a new infrastructure; a physical space; new instrumentation and specialised personnel with the necessary skills to run the test. Once everything was set up, they started offering TPMT enzyme tests, which later evolved into a full PGx service that provided phenotyping as well as genotyping in the cases where phenotyping did not give a clear result, e.g. when there had been a blood transfusion or when the phenotype indicated that a patient was deficient. By doing this, they established a TPMT PGx service.

> *The important thing for us is what we call a service; we don't call it genotyping, we don't call it genotyping, we call it a TPMT service, here we do both (respondent 1).*

5.6.1 Centralisation of TPMT Services

The centralisation of services in two reference laboratories has concentrated the expertise around TPMT testing and has enabled the improvement of protocols as well as the delivery of a PGx service.

The London laboratory started doing TPMT enzyme testing at the beginning of 2000 and the Birmingham laboratory did the same in 2003. That same year, the Department of Health published a White Paper (DoH White Paper 2003) announcing an important investment and implementation plan for genetic services in the UK. Previously, in 2001, the Secretary of State for Health announced a £30 million package of new investment in NHS genetic services (Milburn, 2001). In conjunction with the "foresightful" vision of some geneticists towards the potential of genetic testing, this was a driver in setting up TPMT services in the UK (respondent 11).

5.7 Phenotyping or Genotyping?

Phenotyping seems to be the best way of measuring the potential risk of suffering myelosuppression caused by 6-MP and AZA. The enzyme assay gives more information about the risk of suffering ADRs than the genetic assay, which only looks at the most common polymorphisms that affect drug response, although not all. Not all the polymorphisms that influence drug response are known and even if they were, doing a genetic analysis of all of them would be too costly and too lengthy. For this reason, genotyping remains an option when phenotyping does not give a conclusive answer. At the moment, phenotyping gives results in a few hours and provides feedback to doctors in 6 working days, whereas doing a genetic analysis (only the analysis) takes a few days. In addition, the phenotype can give information about how environmental factors affect drug response, because external factors can alter the inherited pattern of TPMT activity and the levels of TPMT in the blood. For example, even if we are genetically normal metabolisers of the drug, under other additional drug treatments we may become slow metabolisers (because drug interactions may decrease the "normal" levels of TPMT of a particular patient) and so we may become susceptible to adverse events even if, in normal circumstances, we would not be susceptible. This is something that only the phenotype can predict (respondent 6) and, in these cases, the laboratory recommendation is to go for phenotyping (respondent 1 &3).

…If you get the phenotype wrong, it doesn't matter whether you've got a fantastic technology to analyse the genotype…you have to make sure that the phenotype is right…(respondent 13)

However, it is unclear how all the environmental factors will influence AZA response and how these could be assessed in the laboratory. Drug response, apart from having a genetic component, is influenced by general health, gene-gene interactions and drug-gene and drug-drug, interactions. So adverse reactions might appear because of a genetic predisposition, but also because of behavioural conditions that may expose an individual to mutagenic agents and this is something that needs to be integrated into any further PGx analysis. PGx (in this case TPMT testing) may be useful in some cases but it is not clear in all cases and, at the moment, the use of TPMT testing seems to rely on the pay-off between the risk of having a chronic disease and getting worse because of it, versus the risk of suffering an adverse drug reaction (respondent 13). For this, genotyping is particularly important:

- After phenotyping, when a patient has been diagnosed with low TPMT levels the genetic test helps to make sure that the phenotype assay is exactly right.
- After a blood transfusion because the TPMT concentration of the patient and the donor are different and measuring the levels of enzyme is not an accurate measure.
- When the measure of the phenotype does not show a clear result.
- When a patient develops an adverse drug reaction because he/she has been inappropriately treated. Also, when a patient takes the drug and afterwards the treatment is withdrawn and then re-started a few months later, which also affects drug response.

The way in which the reference laboratories provide the service is first to do the phenotype and if the result falls into an area of uncertainty, if the patient has received a blood transfusion or the patient has no or very low levels of TPMT, then they would also do the genotype. The benefit of genotyping is that, whatever result you have, you get it for life, although the disadvantage is that, even if you have an unchangeable genetic profile, the phenotypic expression of that genotype can be influenced by other external factors that can alter the "normal" TPMT pattern of a person and this alteration can only be detected

through phenotyping. So, while the genotype lasts for life, the phenotype may change according to environmental conditions (respondent 10).

> *If you are deficient and have no TPMT in your blood because the DNA isn't expressing the DNA activity, you know you shouldn't give the patient the drug. But if you are heterozygous (and you are likely to have normal or slightly lower than normal levels of TPMT) but for whatever reason your level of enzyme is very low and some of that has to do with the DNA, then the phenotype gives you much more information than just the genotype. Because the phenotype gives information about what is happening in the body at every moment, and the phenotypic response is the result of a genotype but also of the environment (respondent 1).*

For all these reasons, the two technologies seem to coexist, rather than being substitutes for each other.

In order to investigate further the implications of genotyping on service delivery, the Department of Health awarded funding to the North West Genetics Knowledge Park, to investigate the benefits of genotyping over phenotyping before prescribing AZA across the clinical specialities of dermatology, rheumatology and gastroenterology (NOWGEN, 2005) (respondent 13). During this trial, they were not the reference laboratories, but National Genetics Reference Laboratory (NGRL), who offered TPMT testing. In parallel to what NOWGEN was doing, the NGRL was interested in doing a pilot study (on TPMT testing) in a small region (respondent 14).

5.7.1 Drug Dosing

One of the issues still under discussion is how much TPMT testing can contribute to adjusting the doses of AZA and 6-MP based on the phenotypic and/or genetic profiles. It is known that:

- When a patient has very low levels of TPMT or is homozygous for the low level of TPMT allele, then the treatment with AZA or 6-MP should be interrupted because that patient is at a very high risk of suffering a severe ADR.
- When a patient has lower levels of TPMT than normal, it is likely that he will develop an ADR so clinicians usually reduce the standard dose in these patients (1.0-1.5 mg/kg/day for 6-MP and 2.0-2.5 mg/kg/day for AZA).

- If a patient undergoes a genetic analysis and is heterozygous, there is no certainty that he will have lower TPMT levels than normal, he may or may not. In these cases, as a precaution, clinicians may reduce the dose of AZA or 6-MP, which is currently in a range of 1 to 3 mg/kg a day. However, if the patient had normal TPMT levels while having a heterozygous genotype, he would be receiving a dose below the therapeutic value.
- Finally, when the patient is homozygous or when he has normal TPMT levels in the blood, he will receive the standard drug dose.

5.7.2 TPMT Testing as a Prognostic Test

Genetic testing is currently used as a diagnostic tool either as a confirmatory test to determine if somebody is at risk of a genetic disease, usually single gene disorders, or as a predictive tool to establish whether someone has a predisposition to a disease or is at risk of an adverse drug reaction. However, the current evidence does not yet justify the use of genetic tests to determine how a disease may evolve and it does not yet represent a robust tool for disease prognosis (respondent 1). With time and more research, it might be possible that at least some genetic tests may move from the diagnostics into the prognostics area, although this has not yet happened in the case of TPMT testing (respondent 23).

5.8 Clinical Guidelines

While the reference laboratories advocate the use of TPMT testing to avoid AZA and 6-MP associated ADRs, TPMT testing is not systematically used in clinical practice because no NICE guideline recommends its use and, as a consequence, the test is not reimbursed by the NHS (for more information about NICE and the NHS reimbursement see section 3.3.3 and 8.3.2). This is partly because thiopurines are off-patent and open to generic competition (Woelderink et al., 2005) and NICE tends to focus on new drugs rather than old ones. At the same time, the pharmaceutical industry is more interested in applying PGx to drugs that are being developed rather than to drugs which are 10-50 years old (Human Genetics Commission, 2002). The test might be more expensive than the drug and NICE would probably not appraise it, because a test for a generic drug would not exactly be a completely new PGx application. And without NICE approving the use of a drug or a test, the incentives for implementation by the NHS are reduced.

However, despite the fact that NICE has not formally recommended TPMT testing, the demand for TPMT testing was triggered by the TPMT reference laboratories, which started providing services in 2003. The estimated number of AZA-treated patients in the UK each year is between 30,000 and 40,000. From these, approximately 50% receive TPMT testing in the UK. In 2006, approximately three years after TPMT services were made available in the UK, the London laboratory performed 10,931 TPMT assays, while the Birmingham laboratory performed 11,167 tests between April 2006 and April 2007 (Gurwitz et al., 2009). This level of demand was partly because of clinical professionals who acknowledged of the importance of TPMT testing.

Therefore, TPMT testing faces two hurdles:

1. Deciding whether or not to test since there are no clear NICE guidelines.

2. Deciding whether to use a phenotypic or a genetic test.

5.9 Professional Guidelines

Professional guidelines are strong drivers for technology adoption. For this reason, despite TPMT testing never being appraised by NICE, it was granted approval by some clinical groups. The first group of clinicians that recommended TPMT testing was the British Association of Dermatology (Anstey et al., 2004). As a result, all dermatologists across the UK now refer their patients for TPMT tests before prescribing AZA. Subsequently, the British Society of Rheumatologists considered setting TPMT testing recommendations and, although they have not done this yet, the demand for the test by rheumatologists has increased (Payne et al., 2007). The case of the British Society of Gastroenterology has been different as they have never considered establishing testing recommendations, arguing that AZA has been proven to be safe enough (Carter et al., 2004).

The case of ALL is different. Every child diagnosed with ALL enters into a clinical trial, the UK ALL 2003 (Medical Research Council, 2003), in which TPMT testing is undertaken as part of the trial protocol in order to assess optimal treatments for the disease. So every haematologist treating ALL patients refers them for a TPMT test, although the clinical opinions about its benefits vary. While some haematologists consider that the test is worthwhile (respondent 27), others think that it serves to detect an ADR that could be detected otherwise through routine blood monitoring (after the patient had taken the

drug), because TPMT testing at the moment does not replace a full blood count and electrolyte analysis (respondent 24).

5.10 TPMT Testing Pre-Screening Policies

Besides the clinical implementation of TPMT testing in dermatology and haematology (as part of the ALL 2003 clinical trial), and its partial implementation in rheumatology, in general TPMT testing is not systematically used at an NHS Trust level. Since NICE had not appraised it and TPMT testing is not reimbursed by the NHS, a decision has to be made by the NHS Trust or a particular clinical department within the NHS Trust as to whether they want to cover the cost of the test (£30/sample approximately). Some hospitals in the UK (the minority – approximately 20 NHS Trusts) have established TPMT pre-screening policies, meaning that they have implemented TPMT testing and cover the cost of the test.

NHS Trusts are the UK health purchasing unit, a system which was introduced to improve access to health services. However, the intention of improving health services by a NHS Trust system resulted in differences in management and inequalities of access to some health services (Attridge, 2006). This explains why TPMT testing is reimbursed locally only in some NHS Trusts. Local decisions on TPMT testing are based on the willingness of the Trust to pay for the test and this depends on the cash balance of the Trust as well as on other factors such as the clinician's willingness to prescribe the test (which often depends on their personal experience -respondents 4 & 25), or the proximity to a testing laboratory (through which they receive information about the benefits of TPMT testing).

The lack of formal guidelines for TPMT testing leaves pre-screening procedures up to the criteria of professional associations, NHS Trusts or individual clinicians who foresee a benefit in the test. Clinicians, who support the use of TPMT testing as a routine monitoring practice before prescribing AZA, maintain that it would avoid unnecessary deaths.

> *…there is little evidence in the literature which says that treating patients with AZA is killing patients, but there is some evidence…In one case we did the testing and the patient was deficient; then we called back to the hospital to ask for another sample to do the genotyping, but the patient had died (respondent 1).*

Individual directorates struggle to pay for this because it's quite expensive. So for example in our hospital what I know from one or two directorates is that they wanted to do it but find that they just can't afford to do in the number of patients that are starting on azathioprine (respondent 22).

But in contrast to the arguments of the technology supporters, some of the reasons that clinicians argue against doing a TPMT test are the following:

- In the case of ALL, TPMT testing does not replace traditional screening procedures (such as white cell counts and electrolyte measurement which ALL patients have to undergo anyway) that also assess the patient's evolution once he/she has entered into a thiopurine treatment. So, the introduction of TPMT testing would be an add-on to the current testing procedures, doubling the economic burden of detecting adverse events once the drug has been taken.
- The majority of adverse events that require hospitalisation could be avoided with better prescriptions from clinicians in terms of dosage and better follow up of medications by patients (Pirmohamed et al., 2004). In this context, if the root of the problem associated with ADRs is the clinical prescription procedures, then TPMT testing could prevent, in an efficient manner, only a minority of patients that are at risk of a severe ADR.

5.11 Is TPMT testing a Good Medical Practice?

Once a NICE guideline has been released, NHS Trusts need to implement it within three years of the release. However, although for some people NICE seems to have brought a certain degree of "common sense" to the choice of treatments, for other practitioners, the role of NICE has been contested and not well understood (respondent 1 & 21) as, according to what they say, the same standards do not apply across all therapies. In addition, too much bureaucracy in the process of technology appraisals slows the process and represents a hurdle for existing treatments, which does not allow the appraisal of new therapies (respondent 20 & 24). TPMT testing is a case where the lack of NICE guidelines has caused implementation to be contested.

As was explained in Section 5.9, TPMT testing is a case where clinicians are driving the use of the test.

> *The demand normally comes from the clinicians. There is no point setting up a test for which clinicians will not be able to pay, and the payment of genetic testing is actually quite a difficult area, because there are not many disciplines that are funded for it by the local purchases (usually the Trust or the Region) (respondent 14).*

The test, which has not been appraised by NICE, has had different levels of uptake in dermatology, rheumatology and gastroenterology. While the British Association of Dermatologists recommends its use (Anstey et al., 2004), the situation is different in rheumatology and gastroenterology. Rheumatologists recommend TPMT testing, in the treatment of lupus in particular, depending on the severity of the adverse events caused by the drug, the balance of the costs of the drug and the test, and on the availability of alternative treatments. Biologicals can emerge as competitors to thiopurines, as they overcome the drawbacks of these drugs. In rheumatology there is evidence of a growing interest in TPMT testing, at least for lupus, but not so much for rheumatoid arthritis, where the biological anti-TNFα appears to work well. The increasing interest in TPMT by rheumatologists has been influenced by the TPMT guidelines in dermatology (Payne et al., 2007).

Currently, not doing a TPMT test in rheumatology, even in a minor number of cases, would not be seen as malpractice, whereas in dermatology, not doing the test would have to be highly justified. Therefore, in the lack of formal guidance, coming either from NICE or from the clinical associations, there is a certain leeway in terms of the actions of physicians.

> *[…You have to swim directly against everybody else within your specialty virtually to be accused of malpractice… and as long as a minority justifies its actions, then, not doing the test wouldn't be seeing as doing malpractice] (respondent 22)*

Treatments are put into guidelines on the basis of what the committees think is good enough evidence. For example, the British Association of Dermatologists think the evidence is good enough to justify implementing TPMT testing, while the rheumatologists are still thinking about it and gastroenterologists have not even considered it. Some professional groups are further ahead than others on this; partly because the cost-benefit equations differ among disciplines and there are different sets of criteria of what is an acceptable risk in, for example, dermatology, rheumatology or leukaemia. According to this, some literature argues that the introduction of tests, such as TPMT, needs to be weighed between their drawbacks and benefits (Martin et al., 2006), and this may be not be as

essential in dermatology or rheumatology as in ALL. It may then be easier to justify the use of testing to avoid ADRs in some conditions than others (respondent 6). If the patient's condition put their life at risk, such as in the case of leukaemia, then the TPMT test may be justified more than in other minor conditions, where taking the risk of prescribing a drug with a potential danger of originating a serious ADR, would outweigh the consequences of the disease itself (respondent 6). In other words, patients and clinicians may think that it is justifiable to take severe risks in treating fatal diseases, such as leukaemia, but would not justify taking such risks in other chronic diseases that, although also important, do not put patients at risk of death.

Even when there are no formal mechanisms that recommend TPMT testing, there may be a body of literature that justifies its use. So, as Adam Hedgecoe explains in the case of Alzheimer's disease/APOE testing, the "narrative of evidence" to which NICE subscribes, contrasts with the "narrative of politics" (Hedgecoe, 2004), which, in the case of TPMT testing, is articulated by different clinical associations and some NHS Trusts. A similar situation is seen in the case of the hypersensitivity test for abacavir (Ziagen®). If a patient dies from hypersensitivity to the drug, it might be difficult to defend somebody who does not do an abacavir (Ziagen®) test before they prescribe the drug.

> *…It is not in the drug label but it's out there in the literature; the HIV association guidelines say that this test is available, they don't say "you should do it", they just say it is available. That could be difficult to defend in the court; I would find it difficult to defend not prescribing an abacavir test, knowing what I know and as long as it is in Caucasians… (respondent 13)*

So, in answer to the question of whether TPMT testing is good clinical practice, we can conclude that there exists a strong correlation between what NICE considers good medical practice and the demand for technology. At the same time, there is also a correlation between what clinical associations recommend and the degree of technology adoption. The dilemma emerges when the opinions of NICE and the opinions of clinical groups differ. Although NICE guidelines are statutory and need to be implemented in the clinic, clinical practice is strongly controlled by clinicians and, in this context, peer opinion is very persuasive. Such was the case in dermatology, where TPMT testing was widely implemented even when NICE did not make specific recommendations. In cases like these, the innovation pattern is more bottom-up (respondent 10), led by the clinicians, and in opposition to top-down approaches led by regulators such as NICE.

However, the boundaries of good medical practice still remain blurred in the case of TPMT testing, which at the moment depends on clinical opinion, individual decisions at a Trust level and recommendations from clinical groups. In the future, it may be that, as happened with other drugs (such as abacavir), it will become difficult to justify not doing a TPMT test before prescribing AZA because there is some literature that explains that it is useful. Further support for TPMT testing may also come from the results of ongoing trials, such as the TARGET study (NOWGEN, 2005), which may shed some light on the clinical validity and cost effectiveness of the test, and may inform future testing decisions more clearly.

> *Things get into guidelines on the basis of what the committees think is good enough evidence. So the British Association of Dermatologists think the evidence is good enough to use it whether rheumatologists are maybe thinking about it but haven't done so yet. Gastroenterologists are also thinking about it and neurologists would not even consider it. Clearly one of the issues you have to consider is "how good is the evidence?" If the evidence wasn't good enough, the DoH wouldn't fund NOWGEN to do this Randomised Controlled Trial (the TARGET study), and the randomised controlled trial actually gives us the best degree of evidence to be able to show the utility of a particular genetic test or particular phenotypic test. The problem that we have faces lot of areas and not just pharmacogenetics. The problem is that diagnostic tests are often taken up in clinical practice without very good testing carried out beforehand, and that is a crucial issue for diagnostic tests in general (respondent 24).*

5.12 "Home-Brew" TPMT Tests and Laboratory Accreditation

TPMT testing in the UK is offered by the two UK Reference Laboratories in the form of "home-brew" tests. Both the London and Birmingham laboratories are accredited by bodies that certify their capacity to undertake diagnostic testing (the test is "CE" marked). These bodies are: the United Kingdom Accreditation Service (UKAS), recognised by the Government as the national accreditation body, which is the signatory of international mutual recognition agreements on behalf of the UK, and the Clinical Pathology Accreditation (UKAS) Ltd (CPA), the licensing organisation in the UK for accrediting laboratories. The two entities have formed a partnership where they co-operate on building consensus on accreditation standards for laboratories in the country (UKAS, 2008), which is important to assure the harmonisation of testing procedures. Although not all laboratories in the UK need to be registered within the accreditation system, those who are registered guarantee that the tests that they provide comply with the European quality control standards ISO 17011 and ISO 9001. These standards relate to operating procedures, instructions and forms of providing a service, maintenance of the equipment and other

resources, staff recruitment and training, as well as customer satisfaction (CPA, 2008). However, they do not look at the clinical validity of the tests, which leaves a gap in what could be considered to be an acceptable standard of clinical utility (see the concept of clinical utility in section 3.3.1). So, while laboratory accreditation is obtained on the grounds of good laboratory practice, clinical utility remains one of the major problems that underpin the lack of harmonisation in testing procedures.

> *The key issue is to demonstrate their clinical utility, but there are not many models out there where clinical utility can be demonstrated (respondent 14).*

In the case of TPMT genetic testing, laboratories usually look at the three most common polymorphisms that influence the response to AZA or 6-MP. However, there is not a validated protocol to that effect. Because they are the three most common polymorphisms, genetic tests should be restricted to those three. In other countries, like Spain for example, genetic testing targets 21 polymorphisms implicated in drug response and, at the moment, none of the procedures can be considered inappropriate since a validated standard procedure for TPMT genotyping has not yet been developed.

The obligation to send samples to accredited laboratories depends on the in-house regulations of each hospital. Although most predictive genetic testing in the UK is quite well covered by accredited laboratories, sometimes, when no one else offers the test, public laboratories need to send samples to non-accredited laboratories (in particular for rare genetic conditions). In these circumstances, the results should be treated with extreme caution and interpreted in the context of the individual patient (respondent 14).

In Mendelian disorders[10] (single gene hereditary conditions), the UK Genetics Testing Network appraises the clinical validity of these tests, but there is not a similar body for PGx. In the rest of genetic testing all that is required is to have a CE marked assay, which proves that the test is technically accurate. As long as the description of what the test contains and what the test measures is accurate, and as long as the reagents are made in a quality

[10] Mendelian disorders refer to conditions that occur due to an inherited genetic profile, such as Huntington's disease or Cystic fibrosis. Other conditions are due to alterations in the normal DNA sequence, as a consequence of a mutation. These last conditions are not inherited, but acquired during the lifetime.

controlled manner, the IVD regulation does not require further regulation in terms of getting that test onto the market.

5.12.1 TPMT "Home-Brew" Markets

In the UK, the test for TPMT analysis was one of the first PGx "home-brew" assays offered and sold on an open market (respondent 1). A similar test had previously been marketed in the US by *Prometheus. Prometheus* was granted two US patents in 2002 and 2004: one for a TPMT enzyme test and the other for a TPMT genetic test, although *Prometheus* does not hold a European patent for TPMT testing, probably because a market for home-brew tests already existed in the UK (as well as in Europe) (Zika et al., 2006). However, even though the testing market in Europe is dominated by "home-brews" or LDTs, if the situation ever changed, European laboratories would not seem to be sufficiently prepared to deal with gene patents, and would require more support to negotiate the patent landscape around them (Hopkins et al., 2008, Gaisser et al., 2009).

Some of the interviewees argued that laboratories offering "home-brew" diagnostic services should be working to equivalent standards to companies developing IVD tests (because at the moment the IVD Directive does not cover the development and use of "home-brews") and suggested that the difference between IVD and "home-brew" tests should be in the implementation of those standards (what you do with them and how you deliver them) (respondent 14).

While TPMT testing remains a "home-brew" market in Europe, it does not in the US. In the US, *Prometheus* (California), who is the holder of the TPMT patents, recently sued the Mayo Clinic (Minnesota) for patent infringement. The Mayo Clinic does the same type of testing as *Prometheus*, but does not have a patent (they do a "home-brew" test). The Mayo Clinic claims that *Prometheus* patents are based on mere observations and that such "observational patents" add to health care costs and complicate research. Prometheus, with the support of the American Intellectual Property Association, on the other hand, claims that denying patents could stifle innovation. The case, which arose 5 years ago, is still in the court (Marshall, 2009).

5.13 The Cost of AZA and 6-MP Related ADRs

According to what has been said in this chapter, it is possible to identify, with high accuracy, patients who are at a very high risk of a severe ADR (1 in 300). The immediate intervention with these patients is to not give them the drug. However, it could seem difficult to justify doing (as an estimation) 300 TPMT tests to identify only one person at a very severe risk of ADRs. This estimation changes if we look at the associated costs of treating an ADR as a result of not doing a TPMT test versus detecting who is at risk of a severe ADR (even if it is 1 in 300).

NHS admissions related to ADRs account for 1 in 16, with an estimated cost to the NHS of up to £466m annually and an average cost of ADRs (generally) per day per patient of £995 (Pirmohamed et al., 2004).

If a patient who is among this 1 in 300 takes AZA or 6-MP, s/he could end up in intensive care for 6 weeks (42 days) in the case of a severe adverse event (respondent 22). Taking these numbers and the previous estimation, treating this patient would cost (42days x £995/day =£41,790), while doing a TPMT test for 300 patients would cost (30x300=£9,000). This is a very broad estimation based on the extreme case where a patient suffers a severe ADR; fully analysing the cost-effectiveness of TPMT testing would be more complicated.

According to a cost-efficiency study that analysed the efficiency of phenotyping (Gurwitz et al., 2009), the average cost per identified TPMT-deficient individual (with no TPMT enzyme) is:

- £8,250 for the Guy's Hospital Laboratory, who performed 10,931 phenotypic tests (by MS), with a TPMT-deficiency rate of 1:275. The average cost per test was £30.
- £4,732 for the Birmingham City Hospital Laboratory, who performed 11,167 phenotypic tests (by HPLC) with a TPMT-deficiency rate of 1:169. The average cost per test was £28.

Another estimation calculates that the cost of treating a patient for pancytopenia (an ADR which originates due to a drop in the number of cells in the blood) would be approximately £7,000-£11,200 (antibiotics £100 per day, fungicides if required £100 per day , hospital bed £600 per day, average hospital stay 10-14 days). Based on this, the total cost of screening to detect one patient with deficient TPMT activity is estimated at £2,275 (Graham et al., 2004).

Other economic evaluations have focused on the analysis of genotyping. Six TPMT testing economic studies have concluded that TPMT testing is cost-effective, although the final costs are not the same in each of them (Payne et al., 2009).

There appear to be important differences in TPMT-associated economic information. Two factors should be recognised:

- Cost-effective sources need to be integrated and understood in the whole context of TPMT testing (Payne et al., 2009).
- One of the reasons for these differences might be that ADRs are mis-reported (Gurwitz et al., 2009). In order to establish an accurate economic evaluation, they should be reported more systematically (Compagni et al., 2008). Some examples of this mis-reporting have been investigated. During the period of 1 July 1963 to 19 May 2006, the UK Medicines Control Agency received 1030 ADR reports regarding AZA, and 110 of them were fatal. On the basis of the UK Medicines Control Agency AZA report, one may estimate that the rate of fatal ADRs among AZA users is in the range of 1 per 10,000 patients. However, a later analysis showed that this was not the case. For the period of 1 July 1963 to 31 December 1989, there were 272 AZA-related ADR reports of which 30 were fatal, whereas for the period of 1 January 1990 to 31 August 2007 there were 853 such reports of which 90 were fatal. Thus, true UK statistics of AZA-related ADRs may be up to 20-fold higher than those reported to the UK Medicines Control Agency (Gurwitz et al., 2009).

5.14 Summary

TPMT Testing and the prevention of ADRs caused by Azathioprine and 6-Mercaptopurine in the UK

Thiopurines (Azathioprine-Imuran® and 6-Mercaptopurine-Purinethol®) are immunosuppressant drugs used, since they were first marketed in the late 1950s by Wellcome (later on Glaxo and now GSK), for treating patients undergoing organ transplant surgery. Although these drugs were firstly aimed at avoiding transplant rejection, they were later on used to treat autoimmune conditions, mainly in dermatology, rheumatology, and gastroenterology, and in hematology to treat acute lymphoblastic leukemia.

Thiopurines, as well as any other drugs, have associated side-effects, principally a reduction in the production of blood cells that can seriously compromise the patient's health. Because of this, patients treated with these drugs need to be monitored (full blood count, liver function tests and electrolyte measurements) on a weekly basis, until the treatment is stabilised. Some of the adverse drug reactions (ADRs) caused by thiopurines have been associated with low levels of or the lack of the enzyme Thiopurine Methyltransferase (TPMT) (Black et al., 1998, Arenas et al., 2006) and, according to the levels of the enzyme in the blood, people can be advised not to take the drug or be prescribed a lower dose. The response to azathioprine also has a genetic component and mutations in the gene that codes for TPMT can also be associated with ADRs (Coulthard et al., 2004, Coulthard and Hogarth, 2005, Arenas et al., 2006). However, the correlation between enzyme levels (phenotype) and mutations (genotype) is not very clear and, at present, testing for the enzyme levels is more effective in most cases than looking for genetic mutations, because only some of the mutations implicated in drug response are known (except in patients who have had a blood transfusion).

The major benefit of TPMT testing (phenotypic test) is diagnosing who is at risk of a severe ADR which may be fatal, although it is estimated that only 0.3% of the population might be exposed to that risk. 10% of the population might be at a moderate risk (not as severe) and the remaining 90% may develop a normal drug response. In the UK there are two reference laboratories (within the NHS) that offer TPMT testing to any physician that requires it.

These tests are not commercial (they do not comply with the In Vitro Diagnostics (IVD) Directive that rules the marketing of commercial diagnostic tests) but they are laboratory developed or "home-brew" tests. The use of TPMT testing is not extended across the clinical community (Farguer et al., 2006) and there are different patterns of use between dermatologists, rheumatologists, gastroenterologists and hematologists in the UK (Payne et al., 2007). Additionally, TPMT testing is still not a mandatory practice in the NHS as the National Institute of Clinical Excellence (NICE) has not yet set the guidelines for using the test. As a consequence, the cost of the test is not reimbursed but the NHS and NHS Trusts willing to offer the test need to cover its cost with their own budget. But, although there are no guidelines, the British Society of Dermatologists has said that TPMT testing should be considered before prescribing azathioprine (Anstey et al., 2004), a recommendation also followed by some rheumatologists (Payne et al., 2007). In contrast to the dermatologists and some rheumatologists, the British Society of Gastroenterologists have stated that azathioprine has been widely used in Ulcerative Colitis and Crohn's Disease and has been proved to be safe enough (Teml et al., 2007), so they do not add further recommendations on TPMT testing.

One of the main points that emerge from this case study is the impact of NICE on clinical decisions, but more importantly, the impact of other factors in the lack of NICE guidelines.

Chapter 6. The use of TPMT testing in clinical practice in Spain

6.1 The Unexpected Interest in Off-Patent Drugs

AZA has been, for years, a widely drug used after transplant surgery. First developed by Burroughs Wellcome, azathioprine in Spain is currently commercialised by another company, UCB Pharma (the companies commercialising AZA in Spain have changed over the years).

AZA is a cheap and widely used drug. However, although AZA had benefited from a reasonably stable market for several years, the situation changed drastically when, in 1987, its patent expired in Spain, and, almost in parallel, a new drug, mycophenolate (Cellcept® - Roche). Cellcept® emerged as a competitor to AZA, targeted to "dethrone" it in transplant surgery.

During this time, AZA was commercialised by Medeba, a pharmaceutical company later acquired by Celltech and afterwards by UCB Pharma. Medeba had different drugs on its portfolio in Spain. Most of these products were the result of the acquisition of a small British company owned by Glaxo-Wellcome (the initial developer of AZA). The income from Medeba was reasonably good; however, it had a very old portfolio. The fear of Medeba was that, with the emergence of mycophenolate, the Spanish Health System would prioritise this new drug and withdraw the use of AZA. This was foreseen to Medeba as being relatively easy since Spain lacks of an independent regulatory body, such as NICE in the UK that base reimbursement decisions on cost-effectiveness and, instead focus on newer therapies at the expense of older drugs. These newer drugs could then be very appealing for the Ministry of Health and the Public Administration (respondent 33), and clinicians who prescribe them would get strong incentives from doing so (respondent 30).

In such a situation, AZA had few chances of survival in a market dominated by other newer and more expensive drugs (the treatment with mycophenylate was £228/month and AZA only £20/month) and, Medeba, aware of the situation, started looking for alternative options to cope with a possible market failure of AZA.

> *The health system is interested in implementing policies that have an electoral impact in the short term, and betting for an old therapy when there are newer therapies that the industry and the media are going to sell as new and innovative is very appealing for the Ministry of Health and the Public Administration. Because in Spain we don't have any independent body that assesses new treatments and new drugs, like NICE does in the UK, therefore the decisions are taken by the Ministry of Health, and what they do is they apply (at the lowest possible cost) the newest therapies. So in this case, supporting AZA, which was an old drug, was not "politically appealing". (This shouldn't be said publicly but this is the reality!). This short term electoral view is the reason that many therapies are abandoned that shouldn't be.* ***(respondent 33)***

Medeba then found a series of publications that studied some biochemical aspects of the response to AZA and started thinking on renovating its drug portfolio. The first efforts of Medeba, resulted in the possibility of using AZA in gastroenterology, and not only after transplant surgery, since AZA was already used by gastroenterologists, although this was not indicated in the drug label (the drug was being used off-label in these cases).

At this point, UCB Pharma saw the possibility of changing the business model of AZA and started informing gastroenterologists about their option on its use in gastroenterology. This coincided with the process of changing the indication of the drug to include the treatment of inflammatory bowel disease, in order to avoid competition from mycophenolate (Roche) in the treatment of transplant patients. UCB Pharma at this point had a strong incentive for creating a new market for AZA because digestive autoimmune diseases, such as inflammatory bowel disease, were growing conditions in Spain (respondents 33 & 37).

Even though AZA was very widely used at that time (around 1996), in particular by certain groups of super-specialists, AZA faced some fears (respondent 33):

- There was a perception among clinicians that the drug was not safe enough and could induce leucopenia and severe pancytopenia: clinicians were not sure who was likely to develop these adverse events and when they were likely to develop them; and
- There were dosing problems because, as clinicians feared adverse events, they were afraid of giving high doses of the drug and they often prescribed sub-therapeutic regimes which had very little or no efficacy.

In order to improve the use of the drug, some evidence found in the literature pointed to the possibility of optimising the dosage and therapeutics of AZA, according to the levels of TPMT in the blood(Weinshilboum et al., 1978, Evans and Relling, 1999).

With these findings, UCB Pharma, was not only interested in changing the label of AZA, but also in finding a way to test patients for TPMT and to adjust doses accordingly. So, if drug response was susceptible to changes due to genetic/phenotypic factors, and if pharmaceutical companies added such information to the technical specifications of the drug, then they could force the health system to use the drug under those specific circumstances.

The strategy of looking for new drug indications (commonly used by pharmaceutical companies) was adopted by UCB Pharma through the addition of a PGx component to the "old" AZA..

UCB Pharma then started searching for research collaborators to develop a technique able to measure the activity of TPMT in patients who were under azathioprine. A research collaborator was found in the biochemistry department of a public university (Universidad de Alcala). The university had previous experience in metabolic enzyme research and, after eight months of developing the technique, the laboratory started running TPMT testing. However, it was unclear at that stage who to test, because for gastroenterologists AZA was used off label and so the company was not yet prepared to advertise a drug for a condition that was not on the label. Nevertheless, UCB Pharma decided to start testing for the TPMT enzyme in sufferers of inflammatory bowel disease, in cases where clinicians were already using AZA (off-label). Subsequently it became possible to improve the dose and therapeutic profile of the drug by offering (only for research purposes) TPMT testing.

In the meantime and in parallel to the trial of TPMT testing launched by UCB Pharma, the company was trying to change the label of AZA and get an indication for inflammatory bowel disease. This would justify the use of TPMT testing in these patients.

UCB Pharma finally succeeded in its purpose of acquiring a new indication for AZA, making Spain the first European country to obtain it. Other countries followed Spain and also changed the drug label.

UCB Pharma then started identifying where the biggest demand for AZA was and informed their commercial network about the implications of TPMT testing in drug management. But the company was not yet prepared to recommend an improvement in dose or to assure that the patient who was tested wouldn't suffer from adverse events. Instead, it started offering some information about TPMT testing and training on the use of genetics in clinical practice and provided funding to launch a clinical trial. Since December 1998, the biochemistry

department at the university started measuring TPMT levels and screening patients using a home-brew method based on immunohistochemistry (Gisbert et al.), while UCB covered the cost of the TPMT test: €50 at the beginning and €30 later on.

Most of the hospitals that were approached by the pharmaceutical company, UCB Pharma, entered the trial; although patients were not aware they were being tested (doctors should have asked for informed consent even for treating with AZA, because at the time the drug was not indicated for bowel disease).

The major driver for testing at that stage was the curiosity of doctors to check the levels of TPMT enzyme in the patients who developed myelotoxicity after taking AZA; this did not necessarily mean that they believed what UCB Pharma was saying. The other driver was the problem of managing patients who either did not respond to the treatment or developed an adverse event.

The first results of the trial confirmed that TPMT levels were very low or absent in patients with severe adverse effects, just as the previous literature suggested. After 1998, when 35,000 patients were monitored (Gisbert et al., 2006), the test was offered in other specialities (dermatologists, rheumatologists and neurologists among others), but never to haematologists because in haematology 6-MP is more widely used than AZA and UCB Pharma does not sell this drug.

6.2 Public/Private Interest and the Set-Up of TPMT Diagnostic Services

During the period of the clinical trial TPMT testing was done in a research environment. When there was a large enough volume of samples, the process of testing was industrialised and the technique was transferred into a private laboratory in Barcelona, Cerba International. Since then (2004) the laboratory has begun offering phenotyping and quantification of thioguanine metabolites (TGNs) (6-MP and 6-thioguanine), which would also indicate whether a patient is developing an ADR. At that time a private laboratory set up a service for public hospitals who requested it. The service includes measuring the levels of enzyme in the blood but does not involve genotyping. Another research laboratory did some testing on TPMT mutations and drug response without conclusive results (respondent 30) and so genotyping was never implemented as a service.

The situation at the moment, in Spain, is that TPMT phenotyping is only provided by private companies. It may be possible that in the future, similar services will be set up in a public hospital. However, comparing the Spanish health system with the UK's, the NHS has its own business units (each Trust) and each of them can take their own decisions, whereas in Spain that doesn't occur and budgets rely on Regional Governments. Consequently, service delivery is very much dependent on whether individual regional governments are more or less innovative (respondent 35).

It should be noted here that it was not possible to access to the names of the clinicians who were involved in the TPMT trial. Other clinicians approached refused to be interviewed as they did not have enough knowledge about TPMT testing and its effects on AZA prescription. Some temptative conclusions may indicate that, only the clinicians approached by UCB Pharma were the ones using TPMT testing as a predictor of drug response.

6.3 Lack of Standards and Service Delivery

6.3.1 TPMT Testing in the Laboratory

TPMT testing analysis is perceived by some researchers as a promising field to exploit in the future. Some respondents demonstrate their willingness to expand further the PGx services they provide by adding TPMT testing to their tests portfolio (respondent 31), although a current lack of coordination for TPMT testing, hinder the process:

- There exists an important lack of coordination between clinicians who manipulate samples and send them to external laboratories such as Cerba International.
- The pharmacological and genetic departments within the public hospitals, often, do not have access to samples for PGx testing, because PGx testing is not a routine monitoring (respondent 30).

Some research on TPMT testing undertaken by some geneticists working in a public hospital, intended to assess differences in TPMT genotypes and drug response. This piece of research concluded that testing for mutations on TPMT was not sufficiently relevant to predict ADRs and therefore was not recommendable to implement it as a new service. There were two main reasons for this (respondent 30):

- The majority of the patients that were monitored (70 in total) presented a genotype that was homozygous for the high level of enzyme allele (90.9%). These patients usually have normal or high levels of TPMT and are not at risk of an ADR. The frequencies obtained from the patients that were heterozygous and homozygous for the low TPMT enzyme were 7.8% and 1.3% respectively. Taking into account that it is only the third group (the homozygous for low levels of enzyme) who will benefit the most from this test, by avoiding very serious ADRs, it becomes infeasible to undertake TPMT genotyping for the entire population who undergoes treatment with AZA.
- The number of patients who suffer from an autoimmune disease who can potentially be treated with AZA is small. Data obtained for rheumatoid arthritis, for example, reveals that only 10% of these patients (from a total number of 380 being treated in a hospital) are given AZA (respondent 30).

6.3.2 TPMT Testing in Clinical Practice

As it was stated at the end of section 6.2, the access to clinical opinion was difficult. We could only interview two gastroenterologists who had been involved in the trial, so the statements made in relation to TPMT testing should be assessed in the context of the restrictions in access.

In Spain, if any, the gastroenterologists are the majority of clinicians who do TPMT testing before prescribing AZA. These clinicians started requesting the test, on the basis that the technical specifications of AZA included a paragraph in the safety section that mentioned possible susceptibility to the drug in the existence of TPMT polymorphisms that could be associated with myelotoxicity events. The clinicians we approached (who did TPMT testing) assume that, in patients with very low TPMT levels, the prescription of AZA could be questioned, and in the rest, the full doses could be administered. However, establishing relations between TPMT status and drug dosage remains a critical issue and there are no guidelines or protocols that control the association TPMT levels-drug response (respondent 30).

From a practical or legal point of view, there may be an issue if the clinician does not do TPMT testing and does not screen the patient with a hemogram:

- Every day during the first weeks of treatment; and

- Fortnightly subsequently until the first six months of the treatment are over.

If a clinician does not have regular information regarding patient blood monitoring he might have legal problems. However, while hemograms are an established practice, TPMT testing is not, and not doing a TPMT test does not have the same legal implications as not doing a hemogram. So while not doing systematic hemograms might be a cause for a malpractice suit, in the case that a patient develops an ADR as a consequence of not doing a TPMT test, this might not be a case for malpractice.

In addition to this, TPMT testing is not well standardised because the different laboratories who offer the service use different units to measure the levels of TPMT in the blood and the lack of a standard threshold may lead to misunderstandings in the interpretation of the results. Cerba, being the laboratory with most experience in TPMT testing (it has already tested 35,000 patients), has not acquired the status of a reference laboratory, and this is seen as a risk for UCB Pharma. Still, the lack of knowledge within the clinical community about the benefits of TPMT testing has implications for demand for TPMT testing. Even though there is some demand for TPMT testing in Spain, it is very low compared with in the UK. The fact that there is not a very good understanding of the usefulness of TPMT testing was also obtained during the clinical interviews.

6.4 Pharmaceutical Companies, Guidance and Decision-Making

Once UCB Pharma managed to change the drug label (at the National Drug Agency – Agencia Española del Medicamento) and include its use in gastroenterology, Glaxo also added those relevant aspects of the technical specifications in each other country where AZA was commercialised. However, although the label was changed to include gastroenterology diseases as targets for the drug, the label did not include TPMT testing. Only the technical specifications of AZA worldwide incorporated TPMT as an element of interest for drug response. Changes in label are done either because the regional agency forces the pharmaceutical company to change the label locally (in a country, for example), or because different local agencies get in touch with the EMEA, and show them that they have made label changes in their countries, and then the EMEA can make the change possible at a European level in all the technical specifications of the drug in the different countries in the EU. But commonly these changes are only done at a local level, so there are

drugs that have different technical specifications in different countries in the European Union. And while the large pharmaceutical companies tend to unify the technical specifications and include all the relevant aspects in every country in a single common specification to avoid future problems, small companies do not usually do this.

6.5 Reasons for a Partial Implementation

But even with the information obtained during clinical trials, UCB Pharma never applied for a patent on the TPMT test, although if it had, it could have acquired the rights to do TPMT testing and require mandatory testing before prescribing AZA. The outcome would have been an innovative drug because it would have had an associated test. This could have achieved an increase in the price of the drug, and it would now be protected because it would have a test associated with it. Such a strategy would have assured the exclusivity of the drug for a long time. But this was never achieved in the case of AZA, because the drug was already very cheap and the price decreased even more in June 2007, with the establishment of a regulation that promoted the use of generic drugs and stated that any drug which had been off patent for more than 10 years and did not have a generic (like AZA) should undergo a decrease of 20% in its price. So, although that UCB Pharma had valuable information to "upgrade" the use of AZA by co-developing it with a TPMT test, it never did so and instead transferred the TPMT testing technology to a private laboratory (Cerba International), who would later start doing the testing.

6.6 Technological Enablers and Barriers

Cerba International improved the technique for TPMT testing and, instead of using a radiochemistry method, they started using Chromatography (HPLC) (Gisbert et al.).

There was an attempt to patent the technique for TPMT testing (only the enzyme test and not the genetic test). The technique was first published as PCT (the first step to awarding a patent) by Medeva, but Celltech (its business partner) did not show any interest in applying for a patent for TPMT phenotyping in Spain or anywhere else, and once the PCT expired (after a company requests a PCT patent, it has two years to request a patent, otherwise the information in the PCT is made public), the techniques used in TPMT testing became public knowledge.

The use of more innovative DNA technologies for TPMT testing is under discussion in Spain. Developing a chip that measures TPMT mutations exclusively is not viable economically, because AZA costs approximately €12-15/test and the biochip/test cost €500/test. However, a Spanish company specialising in biochips (Progenika), has developed a prognostic DNA chip for inflammatory bowel disease which includes TPMT mutations. This chip (IBD chip) was a collaboratively developed project between Progenika, UCB Pharma and the gastroenterology service of a hospital that received funding from the 6th Framework Programme. The chip is prognostic and determines the state of the disease.

The IBD chip includes all the known TPMT polymorphisms plus hundreds of other DNA polymorphisms that are involved in inflammatory bowel disease, either in the prognosis or the diagnosis of the disease. According to the results of the chip, treatments for IBD could be improved, although the level of implementation in the Spanish Health System is still low. The future impact of the IBD chip in gastroenterology is not known, because although the price and the slow adoption rate, there is an indication of an increasing interest in, for example, biochips for conditions such as inherited high cholesterol levels (respondent 35).

The future of AZA is uncertain, in particular when new innovative drugs are continuously emerging. Nowadays, big pharmaceutical companies go for biologicals (or biotechnology products that have, in the long term very wide patent protection, not due to the time of protection but due to the technical difficulties of imitating these innovative products and due to the lack of legislation in bio-generics (respondent 33).

6.7 Summary

TPMT Testing and the prevention of ADRs caused by Azathioprine and 6-Mercaptopurine in Spain

The use of TPMT testing in Spain was triggered by a pharmaceutical company, UCB Pharma, which, aiming to renew an old drug portfolio, envisaged the possibility of co-developing the drug together with a TPMT test. This did not happen in the end, although UCB Pharma funded a clinical trial intended to assess the clinical utility of TPMT testing in gastroenterology patients prescribed with AZA. The main outcome of the trial was raising awareness among the clinical community (gastroenterologists in particular) about the benefits of TPMT testing.

At the moment, TPMT testing is used, particularly in gastroenterology in the National Health Service, although there is not a formal guideline that advocates its use. Hospitals willing to do the testing cover their own costs. The test is done by a private laboratory, Cerba International.

Newer testing alternatives (such as the IBD chip), include mutation analysis of the TPMT gene. These technologies are still expensive and not very widely used, although demand may increase in the future.

Chapter 7. EGFR Testing and Future Therapies for Non-Small-Cell-Lung-Cancer

If Chapter 5 was an illustration of the current state of PGx in treating chronic diseases (autoimmune diseases) as well as acute lymphoblastic leukaemia (ALL), Chapter 7 addresses the implications of PGx for the treatment of non-small-cell lung cancer (NSCLC). However, the way in which PGx is addressed in this chapter is not the same as it was addressed in the previous one, because PGx for treating autoimmune diseases and ALL (TPMT testing) is available in the NHS, while PGx for lung cancer (EGFR testing) has not yet reached clinical practice. EGFR testing may offer alternative options for service delivery in the future, but, at the moment, its clinical utility is still under discussion.

The main difference between TPMT testing and EGFR testing (as stated in Chapter 1) is the target of each of the tests. While TPMT testing targets two off-patent drugs (AZA and 6-MP), EGFR testing targets two drugs under development, Iressa® and Tarceva®. These two new drugs compete to enter new markets. In the UK, Iressa® has not been approved and Tarceva® has only been approved as a second or third line treatment.

EGFR polymorphisms might be (they are not yet) an indicator of good drug response to Iressa® and Tarceva®, if the relation drug-test demonstrated sufficient clinical utility to justify a co-development of drug and test. If that was confirmed, then, EGFR-testing could trigger a change in the existing market dynamics of both drugs.

This chapter in going to present the hurdles that Iressa® and Tarceva® face as well as some of the reasons why EGFR testing is not yet an accepted PGx biomarker for clinical use. An extensive part of this chapter is dedicated to explaining the current debates around the use of Iressa® and Tarceva®, to continue by linking these to a potential use of EGFR testing to improve drug prescription.

…in 20 years time we would be referring to the whole Tarceva®/Iressa® story for the development of new drugs and how we get new PGx drugs into the clinic in a National Health Service such as the NHS (respondent 21)

7.1 Lung Cancer

Lung cancer is a major cause of mortality worldwide. In the UK there are over 40,000 new cases of lung cancer every year and 33,000 people die from it. These numbers make this disease the biggest cancer killer in the country (one in six diagnosed cancer patients and one in four deaths) and the one with the highest incidence in Europe (Roy Castle Lung Cancer Foundation, 2007).

NSCLC is divided into three subgroups: squamous cell cancer, often due to smoking but with decreasing incidence in the UK; adenocarcinoma, with an increasing incidence in the UK; and large cell carcinoma (Roy Castle Lung Cancer Foundation and Cancerbackup, 2007a). Although there is not a definitive cure for lung cancer, its current treatments include surgery, radiotherapy and chemotherapy. Surgery is targeted at those patients whose NSCLC is limited to the lung or to the nearby lymph nodes and can be removed. In the cases where the lung cancer has spread to other parts of the body or to another lobe of the lungs, radiation therapy may be used to shrink the cancer and to relieve pain; chemotherapy may be used to treat some patients (Roy Castle Lung Cancer Foundation and Cancerbackup, 2007a).

Current treatments depend on the stage of the disease and the clinical features of the patients, their general health, general fitness, cardiac, renal and liver function, as well as the histological type of the tumour (non-small cell or small cell). These factors guide treatment and the kind of chemotherapy regime used. When a patient has been diagnosed, there are different choices of chemotherapy treatments, which will be decided upon after the patient has been assessed.

In NSCLC, about half of the patients benefit from first line chemotherapy either by seeing an improvement in the symptoms or a better survival rate, but there is no way of anticipating who may benefit from front line chemotherapy and who will not and so all patients have access to it.

Chemotherapy regimes consist of the following (Blackhall et al., 2006):

- First line treatment with a platinum drug (e.g., cisplatin or carboplatin) in combination with a cytotoxic drug (or a drug that kills the cells, as opposed to citostastatic drugs, which control the cell growth (e.g. gemcitabine, vinorelbine, or a taxane). These treatments can extend survival and improve symptoms without an adverse effect on the quality of life. These regimens lead to a response in 30–40% of patients, a median survival of 8–10 months, and a 1-year survival in 30–40%.
- Second line chemotherapy with docetaxel or pemetrexed, which can palliate symptoms and lengthen survival.
- No chemotherapy regimen has proven effective for third line treatment.

Patients most commonly present an advanced metastasic disease, which if untreated, has a median survival of 4-5 months (1 year in 10% of the cases).

7.1.1 Iressa®: a New Therapy for Non-Small Cell Lung Cancer (NSCLC)

In May 2003, AstraZeneca developed a new drug for treating NSCLC: Iressa® (gefitinib). Iressa® was approved by the US Food and Drug Administration (FDA) to shrink NSCLC tumours (see Figure 5.1). The characteristics of Iressa® were rather peculiar: a comparative trial between American and Japanese patients demonstrated the better effects of Iressa® in women than in men, in Japanese than in Americans and in non-small cell lung adenocarcinomas (a type of NSCLC) than in other NSCLCs (Paez et al., 2004). Also, patients who had never smoked responded better to the treatment (Hansen, 2006). According to these results, the drug appeared to benefit, in particular, Asian (probably due to some genetic determinants of ethnicity), female, 'never smokers', although the causes for this were unclear.

In January 2004, NICE, as a part of its Health Technology Assessment (HTA) programme, started an appraisal of Iressa® (NICE, April 2008). The assessment looked at the health and cost benefits of Iressa® as monotherapy for NSCLC, in opposition to the traditional platinum-based chemotherapy first line treatments.

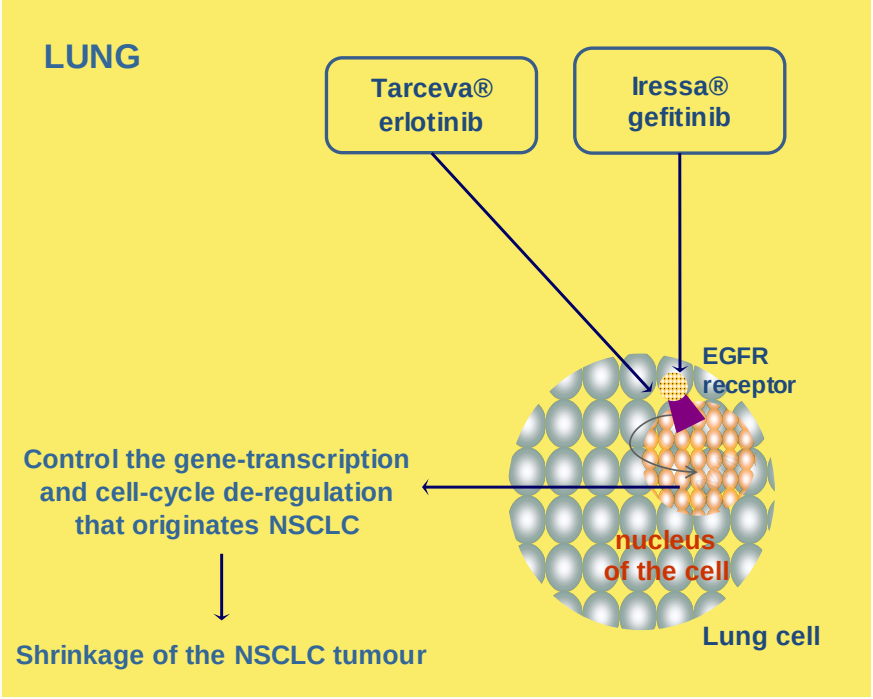

Figure 7.1: Illustration of the mechanism of action of Iressa® and Tarceva®

7.1.2 The European Disappointment and the Japanese Promise

The expectations of Iressa® were high, since it was an innovative drug that could potentially avoid long chemotherapy regimes and promised to improve survival and quality of life. However, in December 2004, the hopes put of Iressa® vanished when AstraZeneca announced disappointing results in the Iressa® Survival Evaluation in Lung cancer clinical trial (ISEL trial 709). This trial, which intended to assess the survival rates of patients treated with Iressa® (gefitinib) (AstraZeneca, 2004). AstraZeneca announced that Iressa® did not prolong survival significantly in the overall population of the study or in patients with non-small cell lung adenocarcinoma. These results took the patients involved in the trial by surprise, since NSCLC had no cure and Iressa® emerged as a promising alternative for these patients. As a consequence of AstraZeneca's announcement, after September 15, 2005, no new patients were allowed access to Iressa®, with the exception of patients that had enrolled in the clinical trial before June 17, 2005 and were already benefiting or had already benefited from the drug (AstraZeneca, 2005a).

The immediate consequence of the failure of the ISEL trial in Europe was the withdrawal of the European Marketing Authorization Application (MAA) of Iressa® (Comis, 2005), which led to the non-approval of the drug in the European territory (FDA, 2004a).

In February 2005, two months after AstraZeneca announced its poor results in the ISEL clinical trial, NICE also announced the suspension of the Iressa® appraisal, in the light of the poor survival rates demonstrated in the trial.

Nevertheless, despite Iressa® was no longer available to patients who had relapsed after first line and second line chemotherapy in many developed countries, 41 trials continued to investigate the clinical efficacy and validity of this agent (18 in the USA, 20 in the rest of the world, and three in Japan) (Blackhall et al., 2006). In fact, this last country took a different trajectory in terms of the evidence provided in the trials.

Although the ISEL study failed to demonstrate better survival rates with Iressa®, prospective subgroup analysis suggested survival benefits in patients of Oriental origin and patients who had never smoked (AstraZeneca, 2005b). This data was taken by the Japanese Pharmaceuticals and Medical Devices Agency (PMDA), who approved Iressa®.

Iressa® managed to get approved in Japan and not in other countries because the PMDA introduced a "fast track" mechanisms for drug approval, although this was highly contested (Sipp, 2004). In fact, families of Japanese patients who died after receiving Iressa® filed a lawsuit against AstraZeneca and the Japanese government, alleging that Iressa® was approved only after five months of review, which they considered as insufficient to show adequate drug safety and efficacy. These actions increased the concern about Japan's growing tendency to introduce "fast-track" mechanisms for drug approval.

Currently, Iressa® is still not approved in Europe, although a recent study revealed that Iressa® proves as effective as chemotherapy in second line treatment (ScienceDaily, 2008). The future implications of this in regards to a possible re-introduction of Iressa® into the UK and theEuropean market are yet to be seen.

7.1.3 Tarceva®: a New Drug for NSCLC Patients

In November 2004, the U.S. Food and Drug Administration (FDA) approved Tarceva® (Erlotinib), a new oral drug, also a tyrosine-kinase inhibitor, developed by Roche in conjunction with Genentech and OSI Pharmaceuticals. Tarceva® similarly to Iressa® was designed to inhibit the tyrosine-kinase activity of the EGFR signalling pathway inside the cell (see figures 7.2 and 7.3) and was licensed for treating patients with advanced or metastatic NSCLC (therefore, as a second or third line treatment) (Genentech, 2007).

The approval of Tarceva® was based on a Phase III clinical trial, known as the BR21 trial. This trial demonstrated a significant survival benefit of Tarceva® versus placebo in advanced NSCLC patients. The trial included 731 patients with second- or third-line advanced NSCLC for whom one or more chemotherapy regimens had failed (Shepherd et al., 2005). The trial showed an improvement in overall survival and demonstrated a 42% improvement in median survival (6.7 versus 4.7 months). Also, 31.2% of patients receiving Tarceva® were alive after one year, compared to 21.5% of patients taking the placebo. Other secondary endpoints, like delayed time to symptom deterioration, improved progression-free survival and increased tumour response rate were also achieved (Genentech, 2007).

Roche, in the light of data from different clinical trials that compared Tarceva® with Gefitinib (Iressa®), docetaxel (Taxotere® commercialised by Sanofi-Aventis) and pemetrexed (Alimta® commercialised by Eli-Lilly), as well as data from the BR21 (comparing Tarceva® with a placebo), claimed that the survival rate after taking Tarceva® was, at least, similar to docetaxel and hence claimed for the replacement of docetaxel (in second-line NSCLC treatment) by Tarceva®. However, although Tarceva® can be used as a second-line therapy, it can only be so when docetaxel is not an option (NICE, February 2007). This decision was taken by NICE, after a contested evaluation of the drug.

7.2 Technology Appraisal

Similarly to what had occurred with Iressa®, Tarceva® also underwent a technology appraisal. For this purpose, NICE appointed two groups of experts: the Erlotinib Review Group, that would conduct the assessment of the drug and, a decision support unit (DSU), who would undertake further analysis of the incidence of adverse drug reactions associated with Tarceva® and who would compare this drug with similar treatments (Roy Castle Lung Cancer Foundation and Cancerbackup, 2007a).

7.2.1 Tarceva® Guidelines

The first Tarceva® appraisal took place in 2007. NICE concluded that Tarceva® should be used (and therefore reimbursed by the NHS) as a second/third line therapy when docetaxel was not an option (NICE, February 2007). Nevertheless, NICE announced it would carry out an early review of the guidance in February 2008 and suggested Roche further research that focused on the response of specific sub-populations to Tarceva®. These sub-groups could be based on two criteria:

- The patient phenotypic status: female non-smokers of South Asian ethnicity suffering from non-small cell adenocarcinoma, as some publications pointed to the association between these phenotypic characteristics and a better response to Tarceva® (Paez et al., 2004).
- The patient's genetic status: based on possible associations between mutations in the EGFR gene and response to the drug (Speake et al., 2005). Some clinical specialists stated that although the link between tumours expressing EGFR and the efficacy of Tarceva® was not yet conclusive, this might be a possible identifier for further patient sub-group analysis. However, their DNA, RNA and protein analysis have not yet given conclusive results on whether EGFR testing can be used as a pharmacodiagnostic to predict drug response (respondent 19).

But in the final appraisal released in 2008, NICE did not change its initial recommendations and concluded that Tarceva® could not be recommended for the treatment of locally advanced or metastatic NSCLC when docetaxel was an option. The conclusions extracted by NICE after the appraisal were based on the following (NICE, April 2008):

- Lack of evidence provided by Roche. NICE considered the assumption of equivalence in overall survival between Tarceva® and docetaxel, proposed by Roche. However, NICE claimed that the evidence from the trials BR21 and TAX317 that evaluated the survival rates for patients receiving Tarceva® and docetaxel respectively, versus a placebo, favoured docetaxel.
- Some part of the analysis of Tarceva® came from two Iressa® trials. According to NICE, there was great uncertainty on the relevance of the Iressa® trials in informing the indirect comparison between Iressa® and Tarceva®.
- The eligible population in the Tarceva® BR21 trial may not accurately reflect the population of patients with NSCLC. In particular, the BR21 trial included a higher proportion of non-smokers than would be expected in clinical practice.
- The effectiveness of Tarceva® in survival terms. NICE discussed the use of treatment duration as a measure of non-progression of NSCLC and improved survival. However, NICE considered the approach taken by the manufacturer to be inappropriate.
- A miscalculation of the costs associated with ADRs. NICE discussed the adverse events affecting patients who were treated with Tarceva® and docetaxel, in

particular alopecia and neutropenia originated by Tarceva®. The Committee considered that the two meta-analyses provided by Roche were less robust because they included unpublished trials with insufficient details about the populations studied. In addition, some of the drugs Roche suggested using to treat patients during the adverse events were not used by the clinicians and NHS Trusts consulted by NICE.

- The administration of the drug. Roche claimed that Tarceva® was an oral drug and it had benefits over docetaxel which had to be given in the form of infusion at the hospital. However, the administration of this infusion lasted an hour and the costs of administering docetaxel were most reasonably considered to lie somewhere between the cost of an out-patient and a day-case.
- Shortcomings in the parameters used to assess cost-effectiveness because Roche did not reflect death as having zero utility. The committee concluded that, taking into account the relative side-effects of Tarceva® and docetaxel, a treatment with Tarceva® was, overall, more costly than treatment with docetaxel. Therefore, Tarceva® was not an acceptable use of NHS resources in comparison with docetaxel.

NICE also took into account the nature of NSCLC as well as the use of NHS resources, and consulted various patients and specialists. This consultation concluded that (NICE, April 2008):

- Patients may prefer Tarceva® because it is orally administered, well tolerated and would require less time in hospital. The favourable toxicity profile and less severe adverse events are particularly important in those patients who do not have other available treatment.
- Clinical specialists appreciated the fact that Tarceva® had good tolerability and this was beneficial, in particular in the lack of treatment options available. The Erlotinib Committee appointed by NICE considered the use of Tarceva® as having a positive effect for patients in whom docetaxel is not suitable or as a third-line treatment after the failure of docetaxel.

Nevertheless, NICE concluded that Tarceva® was not a cost-effective in patients with locally advanced or metastatic NSCLC for whom docetaxel was an option or for those patients who would normally receive Basic Standard Care (BSC) (radiotherapy,

chemotherapy, surgery or a combination of the three) and, as a consequence, could not be recommended for the treatment of locally advanced or metastatic NSCLC.

7.2.2 The Appeal to NICE's Technology Appraisal

NICE's final appraisal determination faced the opposition of three clinical groups: the British Thoracic Society, the Royal College of Physicians and the Association of Cancer Physicians, as well as from patient associations such as the Roy Castle Lung Cancer Foundation, Cancerbackup and the manufacturer, Roche.

> *It's frustrating not to have Tarceva® available for non smokers because in the trials the patients we have who have done well on tarceva and Iressa® are almost exclusively never smokers and they survive for years longer than expected. So if you did a cost-effectiveness analysis it would be positive, very positive for that group. So for that group I don't think molecular predictors are so much an issue. Molecular predictors are an issue for the larger group: the smokers (respondent 21).*

Some of the reasons for their opposition were:

1) Lack of consultation before the final technology appraisal

Roche believed that, a requirement for fairness should have included the opportunity for consultees to respond to the report prepared by the expert review group (ERG) before it was finally considered by the NICE's Appraisal Committee. In the case of Tarceva®, a Pre-meeting Briefing report (PMB), prepared by NICE, summarised the Evidence Review Group Report (ERGR) along with its many criticisms of the manufacturer's submission, failed to report adequately the evidence presented by the manufacturer which addressed many of these criticisms. Roche thought that NICE acted unfairly in not preparing a scoping meeting for the purposes of the appraisal (Roche, 2007).

Patient groups also contended that the Appraisal Committee did not consult relevant stakeholders on the scope of the appraisal, thus denying the right of consultees to comment on the appropriateness of the questions asked within the appraisal (Roy Castle Lung Cancer Foundation and Cancerbackup, 2007a).

2) Lack of standards for appraising technologies

Roche thought that the Appraisal Committee had relied upon supplementary, unpublished, utility analysis carried out by the Evidence Review Group (ERG) but not consistent with NICE's own guidance on the methods for technology appraisal. Some of these utility

analyses included economic models and curve mapping software used to re-estimate the survival rates of patients receiving Tarceva® or docetaxel, which, according to Roche, had been requested but had still not been received. Additionally, Roche claims that NICE provided no explanation to justify rejection of the survival analysis presented within Roche's submission and reliance upon the supplementary analysis produced by the ERG (Roche, 2007).

3) The Product License is not only restricted to third line treatment

The marketing authorisation for Tarceva® allows its use both as a second and a third line treatment. However, Roche claims that the appraisal gives the misleading impression that Tarceva® is only appropriate for third line treatment, and this may have influenced the use of Tarceva® by clinicians (Roche, 2007). Some recent studies advocate that Tarceva® represents the best third-line option in recurrent NSCLC, and could also be used as a second-line treatment in patients who are unsuitable for chemotherapy (de Marinis and Grossi, 2008).

4) Tarceva® is promising because there is a current lack of alternatives for improving survival

Patient groups claim that NSCLC patients are given treatments with very poor outcomes, with a median survival of 6 months or less. Tarceva® is promising because it increases this average in some cases even to survival for more than a year (British Thoracic Society, 2007). Docetaxel survival results reveal that survival in the TAX317 trial (that assessed the survival rates for docetaxel versus a placebo) was 8.9 months (based on peer-reviewed and published data), and in the JMEI study, 8.7 months (based on patient-level data). Survival due to Tarceva®, based on the BR21 trial, was 9.6 months, and this is higher than docetaxel (Royal College of Physicians, 2007).

Additionally, 19 months after the TAX317 docetaxel study started, all the patients were dead. At the same point in the BR21 trial (which led to the approval of Tarceva®), 20% were still alive and 14% were still alive beyond 2 years (Roy Castle Lung Cancer Foundation and Cancerbackup, 2007a). Patient groups claim that this evidence of longer term survival in this particular group of patients is almost unheard of in NSCLC and this is a cause for great excitement amongst clinicians and patients. It seems extraordinary to them that this appears to have been discounted in NICE's appraisal (Roy Castle Lung Cancer Foundation and Cancerbackup, 2007a).

5) In the absence of optimal study results, there needs to be some data to compare treatments

NICE claims that there is currently no direct data that compares Tarceva® with docetaxel. The British Thoracic Society points out the necessity of developing prospective clinical trials that looks at both drugs. However, in their absence, the existing data needs to be extrapolated from the BR21 study of Tarceva® and the TAX317 study, and others (British Thoracic Society, 2007). Roche claims that NICE has taken an approach to dealing with uncertainty that relies on indirect comparisons of data that are unbalanced and clearly favour the existing standard of care. Roche also thinks that NICE acted unfairly by relying on relative survival gain from Tarceva® and from docetaxel, compared with best supportive care (BSC) in BR21 and TAX317 trials. The patients in the BR21 BSC arm had more patients of a poorer Performance Status (2 and 3), thus biasing this comparison in favour of docetaxel (Roche, 2007).

6) The data gathered from previous clinical trials has been analysed in favour of docetaxel

Roche claims that NICE did not provide evidence to support the statement that the BR21 trial is not representative of UK NSCLC patients receiving second line treatment, by virtue of the percentage of non-smokers included. Roche claims that the reference to the imbalance in the percentage of non-smokers across the trials is a reflection of the Erlotinib Review Group and was not reported anywhere in the manufacturer's submission (Roche, 2007).

7) Tarceva® can prevent serious adverse drug reactions that docetaxel cannot

Febrile neutropenia (FN) is by far the most serious hazard associated with docetaxel therapy and is occasionally fatal. The reported incidence of febrile neutropenia in the trial TAX317 (that investigates docetaxel survival rates in NSCLC) was very low (1.8%). However, other sources report an incidence rate of 6% of toxicity (British Thoracic Society, 2007). Neutropenia, however, is not a problem with Tarceva® (Royal College of Physicians, 2007).

8) Performance status and survival rate has not been taken into account

The single most powerful prognostic criterion for survival in advanced cancers is performance status. This factor invariably outweighs any treatment effect in advanced NSCLC. The BR21 trial enrolled more patients with poorer performance status than did the docetaxel trials, thus any bias from the single most important variable is likely to work

against Tarceva® (Royal College of Physicians, 2007). The Royal College of Physicians believe, however, that the impact of poor performance status and the potential for a long surviving cohort, which Tarceva® confers, has not been taken into account (Royal College of Physicians, 2007).

9) Benefits of Tarceva® mean survival rates but also improvement of quality of life

With all current treatment options survival gain is not the only endpoint of treatment (Roy Castle Lung Cancer Foundation and Cancerbackup, 2007a). Given the poor overall survival of patients with advanced NSCLC and the relatively modest impact of interventions on duration of life, symptom palliation and quality of life (QoL) are crucial for these patients. The appraisal appears to consider efficacy purely a matter of relative survival benefit. However NICE's guidance to manufacturers requires them to present measures of a drug's effectiveness in terms of QALYs (quality-adjusted life-year), a health economic parameter that measures the quality of life gained through health interventions by means of the life expectancy and the quality of the remaining life-years (Roche, 2007). Good evidence for Tarceva® demonstrates effective symptoms palliation and excellent tolerance. Therefore, the Royal College of Physicians claim that the limited account taken of these key strengths of Tarceva® (palliation, good tolerance and convenience) is perverse (Royal College of Physicians, 2007).

> *The other way of benefiting from this drug is by looking at end points…and we know that Tarceva, not only reduces the size of the tumour but also stabilises the disease, and this, if not strictly speaking a response, confirms a longer survival (respondent 19).*

Patient groups are also aware of this and claim that a full scoping process would have highlighted the importance of this appraisal concentrating, not only on survival data, but also on patient centred quality of life issues (Roy Castle Lung Cancer Foundation and Cancerbackup, 2007a). All these form a strong argument for allowing NHS access to Tarceva® (Roche, 2007).

10) Adverse Drug Reactions

One of the major differences (in health economic terms) between docetaxel and Tarceva® is that febrile neutropenia is not a feature of Tarceva® therapy and the costs of dealing with severe neutropenia are crucial for economic analysis (Roy Castle Lung Cancer Foundation

and Cancerbackup, 2007a). According to Roche, NICE failed to consider whether the reduction in the costs of treating adverse events associated with using Tarceva® compared to docetaxel would have an impact on cost effectiveness (Roche, 2007). Roche insisted that NICE failed to act fairly by accepting sensitivity analysis performed on the Roche economic model by the NICE Erlotinib Review Group ERG, which is inconsistent and unclear in its parameter selection, and subsequent values (Roche, 2007).

11) There are no options for patients who cannot take docetaxel

NICE did not fully take into account the potential benefit of Tarceva® for patients who are unable to receive docetaxel treatment (Roy Castle Lung Cancer Foundation and Cancerbackup, 2007a), such as those patients who are allergic to docetaxel (British Thoracic Society, 2007).

12) Easy service delivery

For the Royal College of Physicians, the fact that Tarceva® is an oral therapy is very important in terms of improving quality of life by avoiding hospitalisations. However, they believe that very little of these health service benefits appear to have been taken into account in the appraisal (Royal College of Physicians, 2007).

13) Technicalities and Legal Issues

The fact that NICE's determinations are characterised as "guidance" is immaterial because health care organisations should ensure they conform to NICE technology appraisals. The directions issued by the Department of Health require that funding should be made available for products or technologies recommended by NICE. Otherwise, reimbursement will not be made available. So, the UK Government needs to notify the European Commission of the criteria it will use to determine whether products are excluded from the scope of the NHS. However, Roche argues that these criteria do not include an assessment of cost-effectiveness, which is the main measure on which NICE guidance relies (Roche, 2007).

7.3 Clinical Opinion

The data gathered during the interviews and the mini-questionnaire circulated among clinical 16 oncologists was rather positive in regards to the use of Tarceva®. As pointed out in the methodology chapter, the purpose of this mini-questionnaire was, not to get

statistical data, but get answers to the specific questions that would have been done during an interview but could not be arranged due to the time constrains of the interviewees. As an alternative we sent a set of questions by e-mail.

From the 16 clinical oncologists we approached, we got reply from 8. Five of the clinicians treat more than 250 lung cancer patients every year, two of them treat just over 200 and only one treats approximately 50 lung cancer patients per year. None of them had been involved in the Tarceva® clinical trials but four of them were involved in the Iressa® clinical trials.

All of the eight clinicians agreed that Tarceva® had benefits as second and third line therapy over other available treatments. There was a consensus among the eight that docetaxel had no benefits over Tarceva® and they all agreed that Tarceva® is of easy administration, well tolerated and avoids the side-effects of chemotherapy.

When these oncologists were asked whether Tarceva® had benefits over Iressa®, 7 of them recognised not identifying differences among both drugs; only one said there may be some differences, although these may be small.

When they were asked about a hypothetical situation in which they could prescribe Tarceva® as a first line treatment, five of them recognised they would prescribe Tarceva® considering the current evidence. Three of them said they would prescribe it if there was enough evidence to back it up. Only one recognised not willing to prescribe Tarceva® as a single treatment.

From the interviewees we had access to, and through the data available in the appeals against the Tarceva® appraisal, we gathered that NICE is a major bottleneck in the implementation of Tarceva® as an only agent in second and third line therapy for NSCLC patients. As some of the clinicians suggested, they would prescribe it if NICE did not restrict its use.

> *We see about 700 lung cancer patients a year with non-small cell in the region…we are quite immersed in Tarceva and how we get access to it because it works brilliantly in some patients (respondent 21)*

There are a number of factors that the interviewees and clinicians approached by e-mail considered as potential drivers for changing the existing position of NICE in regards to Tarceva®:

- Clinical trial evidence and prospective trials in selected populations.
- Local decisions in the form of local guidelines
- Consensus with colleagues (peer opinion)
- Acceptability of private insurers.
- Publicity for cases where patients are being denied treatments.
- Pressure from MPs.
- Identification of biomarkers to predict responses and reduction in the cost of testing.

According to these answers, it appears clear that, the implementation of Tarceva® in clinical practice depends, not only on the evidence of cost-effectiveness, but also on other factors. Even if the existing barriers were overcome and NICE recommended Tarceva®, in order to make the drug available through the NHS, NICE should be prepared to implement the adequate reimbursement mechanisms.

> *I am convinced about Tarceva's efficacy, opposed to costs again….but nevertheless NICE base its decisions and recommendations on data and there is always susceptibility involved….so even if an organisation say "this is fantastic and we need to have this opportunity to act on the market and reimburse our patients", this is not the final decision. The final decision is always over NICE and NICE at the moment recommends the use of Tarceva® as second and third line treatment, but, even if it recommended it in other situations, there is no system to reimburse (respondent 16).*

> *NICE at the moment hasn't provided funding to my knowledge for Tarceva®….funding was refused although the Scottish Medicines Committee have approved Tarceva® for second line or third line use… In Scotland the NHS will fund Tarceva®, in England they don't yet. This means that the NHS in England and Wales will not yet reimburse it. Some local authority have got local agreement for the NHS to pay for Tarceva®…So, at the moment, while drugs are going through NICE, it is local health authorities who decide what they are going to do on the basis of the evidence that let the drug being licensed. (respondent 21).*

As regulations stay at the moment, two things need to occur before Tarceva® is used in a wide range of situations than it is recommended at the moment: in first place, as NICE stated in its guidelines, Roche should submit further data, possibly on specific sub-populations. In second place, NICE should implement the adequate mechanisms to facilitate implementation when the data is available.

The following sections will discuss the options that PGx testing (EGFR testing in particular) offers to Tarceva® in terms of widening the existing indications of the drug in the UK.

7.4 Genetic Biomarkers: New Options for Service Delivery

The goal of cancer detection is to provide tests that are easy to administer, low risk and highly efficient. Similarly, the goal of PGx is to provide tests that predict drug response. In both cases, these tests rely on the use of biomarkers.

Biomarkers are particularly important, not only for targeting the right therapy to the correct group of patients, but also for detecting those who will not respond and avoiding prescribing drugs that will have no effect, especially as new and expensive drugs (such as Iressa® and Tarceva®, and similarly, other biologicals) come onto the market (respondent 21).

Before speaking about the relevant biomarkers for Iressa® and Tarceva®, we would present the mechanism of action of both drugs.

Iressa® and Tarceva® are tyrosine-kinase inhibitors; they block the tyrosine-kinase (TK) activity of the Epidermal Growth Factor Receptor (EGFR), a cell-surface receptor that is activated when it binds certain ligands (e.g. Iressa® and Tarceva). When this happens, the receptor becomes "phosporilated" (represented in Figure 5.2 by a "P"), triggering a cascade of reactions that "switches" (or activates) the gene transcription and the normal growth of the cell (see Figure 7.2).

They are therefore similar drugs. Some of the interviewees approached supported this.

> *From my clinical point of view and having worked with both of the drugs in the clinic, they do the same thing to the patient. We have patients who have done brilliantly on Iressa® and brilliantly on Tarceva® and we have other patients who have done badly (respondent21).*

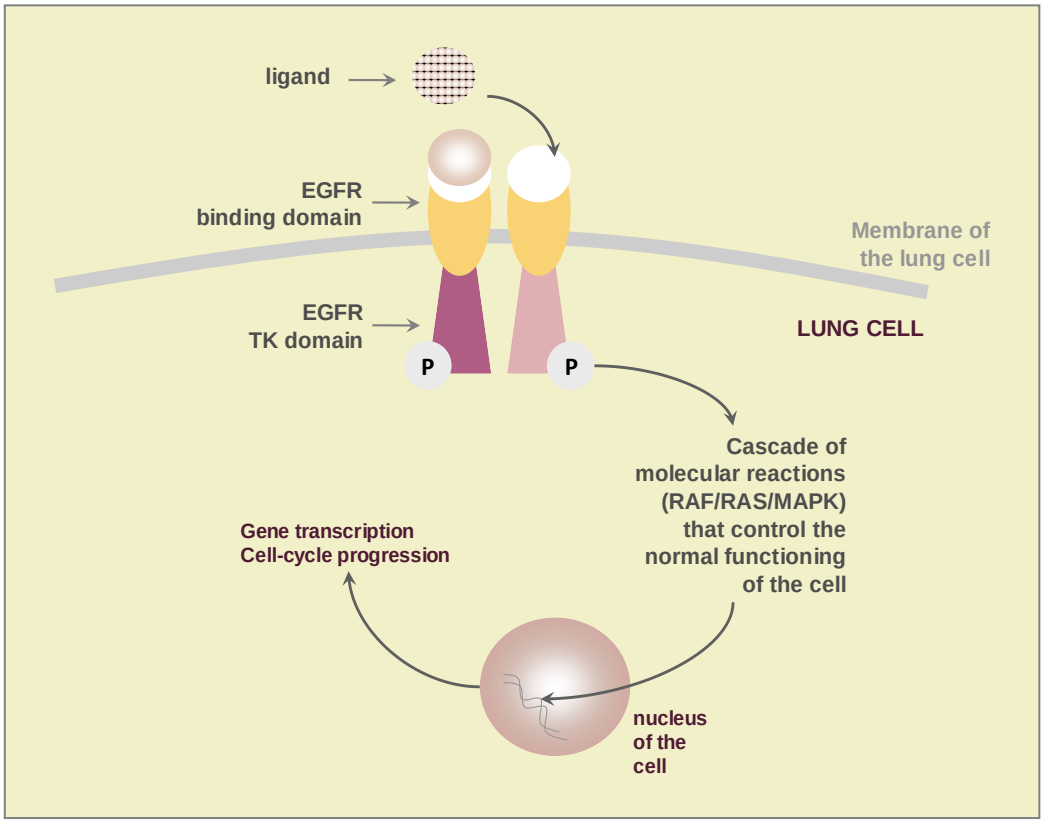

Figure 7.2: Illustration of the molecular pathway and the cascade of reactions triggered by the activation of EGFR.

Some respondents translated this to:

> *Tarceva® was lucky and Iressa® was unlucky (respondent 15)*

> *The drugs are very similar and gefitinib didn´t get licensed and I think AstraZeneca are much more focused now on getting the patient population who is most likely to benefit…because if you are just a little bit unlucky and your sample is diluted with more patients who aren´t going to benefit, your drug can fail by a tiny amount and that is even more costly (respondent 21).*

Mutations on the EGFR gene can alter these normal cell mechanisms and can activate the development of tumours, which origin is changes in the structure of the EGFR receptor. As a result, no ligand can bind to it and no molecular cascade occurs. This alters the gene transcription and the normal cell mechanisms, leading to a series of events characteristic of cancer, such as metastasis of the local tumour or angiogenesis (or the mechanism through which the tumour develops blood vessels to invade the main blood stream), as shown in Figure 7.3.

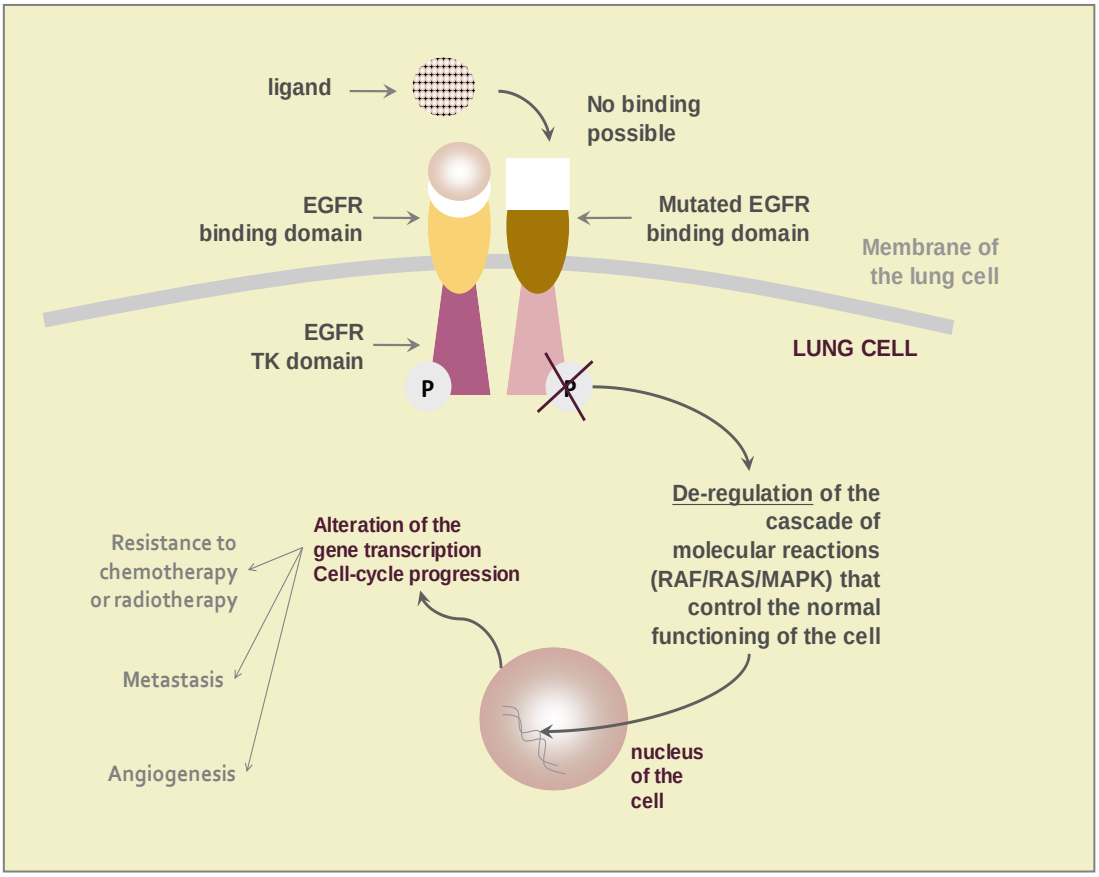

Figure 7.3: Illustration of the molecular and clinical consequences of mutations on the EGFR gene and the alteration of the EGFR binding domain.

Mutations on the EGFR are relevant in the case of Iressa® and Tarceva® because, both drugs are ligands of the EGFR receptor, and, in order to function properly, they need that the EGFR receptor functions accordingly. However, in the presence of mutations on the EGFR gene, the binding domain of the drug is modified and this leads to a malfunction of the molecular mechanisms of the cell and to alterations in the response to Iressa® and Tarceva® (Comis, 2005, Ettinger, 2006). Also, and besides the genetic mutations, amplifications of the EGFR gene (or over-production of the gene, leads to an over-production of the EGFR receptor) can also lead to a malfunction of the mechanisms triggered by the EGFR receptor (although the figure above is only restricted to the mutations).

In the light of the associations between changes in the EGFR receptor and influence in drug response, it was suggested that the detection of the mutations on the EGFR gene could be a predictor of drug response, and a potential diagnostic marker for targeting therapies with Iressa® and Tarceva® to NSCLC patients (Hideharu, 2006). However, the potential of EGFR testing to predict drug response was only discovered after both drugs were already under

developmet (Need et al., 2005). And, at the moment, it is still not clinically validated that EGFR testing could be a reliable predictor of drug response (respondent 19).

As we will see in the following sections, the reasons for this is due to a lack of a full understanding of the physiological response of NSCLC patients to EGFR mutations. For this reason, it is still too early to establish a robust association between mutations on the EGFR gene and drug response, which is the reason EGFR testing, has not yet been approved as a technology to be implemented in clinical practice. Nevertheless, the fact that NICE has suggested that further sub-group analysis should be done before the indications of Tarceva® can be broadened to a wider NSCLC population, indicates the interest in the results of a series of studies which recognise the existence of certain relationships between mutations in EGFR and the response to tyrosine-kinase inhibitors such as Iressa® and Tarceva® (Comis, 2005).

7.3.1 EGFR as a Diagnostic Biomarker

Although that there are no definitive answers to explain the effect of mutations on the EGFR gene on the response to Iressa® and Tarceva®, a remarkable number of patients who have mutations on the EGFR gene have experienced tumour shrinkage after being treated with TK inhibitors like Iressa® and Tarceva®.

However, there is not enough data to establish such a claim as not all the possible mutations in the EGFR gene affect drug response and not all the differences in drug response can be exclusively attributed to these mutations (Ettinger, 2006). Mutations are responsible for 10-20% of the differences in drug response attributable to EGFR; the other 80-90% is due to amplifications of the gene (or the production of multiple copies of the gene the consequence of which is an over-production of the EGFR receptor).

Nevertheless, EGFR mutation analysis is currently attracting the interest of pharmaceutical and diagnostic companies involved in developing diagnostics tests to predict disease susceptibility or drug response.

> *If we believe we have a marker that really discriminates between patient likely to respond and patient not likely to respond, we would use that marker very happily because that is how we improve the way the medicine is affected. We know that every drug will never be 100% effective So, if we can have some marker, some characteristic, something that can predict whether we are actually more likely or less likely to tolerate the drug, that would give us the right information….if we have a marker that is good enough, we would like to use it obviously: we would increase*

efficacy, we would avoid toxicity, and we would be able to make a better case for an extensive medicine by saying "yes it is expensive but look, it actually works in almost everybody who gets it" (respondent 19).

If I was a chief executive officer of a drug company I'd rather have a drug developed into an area where it's going to have the maximum effect; that's what I think anyway (respondent 13)

The rationales behind the clinical implementation of one or the other may be different, especially if the company developing the drug and the test are different. If the company developing the test is a diagnostic company and it is not involved in commercialising the drug, the more tests sold the better.

Most of the time, EGFR testing is going to tell you that the drug is not going to work very well but, if you have lung cancer you are going to die, so if you can have a 10% chance or even a 20% chance of getting a good response to these drugs, you take that for sure. And patients would think like that (respondent 18).

But, when it a pharmaceutical company the one that commercialises both drug and test, there are serious implications for drug sales and, there is a concern that the company would bias some of the results of the research in the benefit of more drug sales.

I think that kind of research needs to be done independent of the drug companies because they have a bias in wanting to maximise drug sales and we don't have that bias. We want to economise as much as we can. So studies like the TARGET trial for TPMT are a way of actually trying to get some evidence in an academic setting (respondent 21).

7.3.2 The EGFR Gene

The EGFR gene is composed of 28 functional parts, or exons, of which the tyrosine-kinase (TK) domain occupies the majority (from 18 to 24) (see Figure 7.4), and it is in this region that the majority of the mutations occur (Shigematsu et al., 2005) - 134 mutations have been identified inside this region (Shigematsu et al., 2005). Out of these hundreds of mutations, only a few, 25 according to DxS[11] data and 28 according to others (Shigematsu, Lin et al. 2005), are implicated in the metabolic response to the TK inhibitors Iressa® and Tarceva®. Therefore, drug response is influenced by only 10-20% of genetic mutations

[11] DxS is a UK diagnostic company specialised in pharmacodiagnostic testing, which has in the pipeline different assays to detect mutations associated with lung cancer.

which, at the same time, account for approximately 13% of the known mutations associated with the EGFR TK domain.

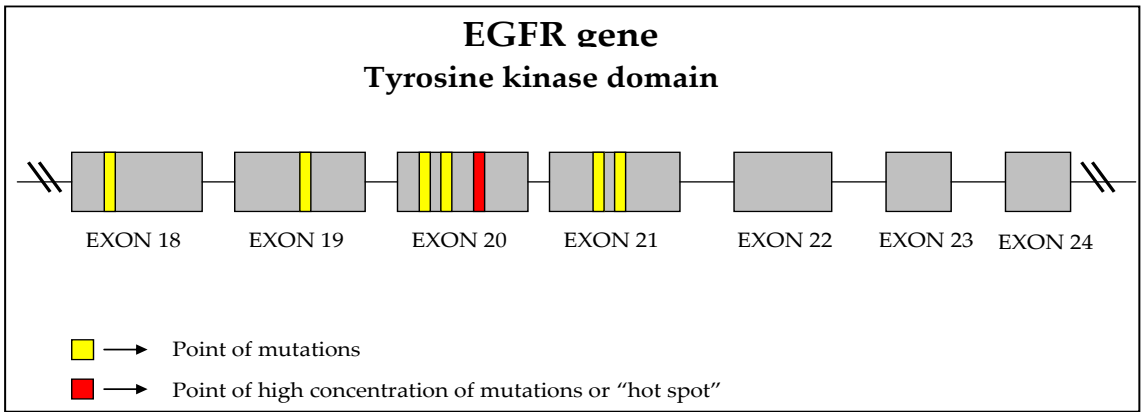

Figure 7.4: Tyrosine Kinase domain of the EGFR gene showing the regions where mutations are more frequent.

There are also mutations in other genes, which might also be involved in drug response. In particular, mutations in the gene K-RAS, also involved in cell proliferation, affect smokers more commonly than non-smokers (Shigematsu et al., 2005). However, the relationship between the K-RAS mutations and the EGFR mutations is not yet clear and hence they cannot be used as joint diagnostic tools.

7.3.3 Service Delivery

As a consequence of the lack of clinical evidence about how EGFR mutations affect drug response, EGFR gene analysis is not a general diagnostic practice in Europe as there is not enough evidence on how patients could benefit from it. But, despite the fact that the NHS does not reimburse EGFR testing for clinical purposes, diagnostic EGFR testing assays are available for whoever is willing to pay for them, although these assays are for research use only, as well as during drug development.

> *For Iressa® and Tarceva®, there are mutation tests but also gene expression levels, protein expression levels, methylation and gene copy number. They are all assays with potential to predict drug response (respondent 18).*

There are different ways of diagnosing the EGFR status of a patient: it is possible to measure the genetic mutations in the TK domain of the EGFR gene, but it is also possible to

measure the levels of EGFR receptor through protein analysis (similarly as with TPMT phenptyping) (respondent 18). For this purpose, different techniques can be applied:

- Traditional Polymerase Chain Reaction (PCR) techniques are not able to quantify the amount of amplified DNA, nor are they able to compare it in real time with a blank.
- In the case of applying genetics, EGFR gene mutations can be measured using different technologies, for example, traditional mutation analysis through PCR or chromosome analysis through Fluorescence In-Situ Hybridation (FISH). PCR measurements require the de-naturation of the DNA and binding with specific DNA sequences which contain the mutations that are being sought. FISH measures the presence or absence of certain DNA inside a chromosome through fluorescence microscopy.
- In the case of applying proteomics, the technology in use is immunohistochemistry (IHC) which, through the principle of antigen-antibody recognition, can detect when a molecule (a drug) has reached its target, because if it has, it will emit a signal that can be detected and quantified.

These technologies are currently being used by diagnostic and pharmaceutical companies, although there are conflicting results from the different ways of measuring the status of EGFR gene/receptor, which makes it unclear which technology is likely to be more efficient for future drug development (real-time PCR, immunohistochemistry or FISH) (respondent 17).

7.3.4 Technological Complexities

Section 7.3.1 introduces the potential of EGFR as a potential predictive biomarker of drug response. The following lines are going to give some of the reasons why, even if EGFR testing was a good predictor of drug response, molecular testing faces other technical complexities.

it is not always feasible to use molecular testing is not always possible because of problems associated with the biopsies of the tumour.

> *The major problems to lung cancer patients are that we don't always good biopsy. We have enough biopsy to say its lung cancer but we don't have enough to do the molecular tests. Also we know from lot of studies that the biopsy might not be the*

same molecular profile as other parts of the tumour, and, you don't want to deny a patient a drug like Tarceva® on the basis of a clinical test, because a clinical test is not 100% accurate (respondent 21).

For either, EGFR genetic or proteomic analysis, samples need to be taken from a biopsy of a NSCLC tumour and this is technologically challenging because the tumour sample is heterogeneous (in contrast to inherited generic variation, the acquired genetic changes associated with cancer arise in a single cell and so a tumour might not be a uniform sample).

In a NSCLC tumour sample, the ratio of the tumour cells to normal cells is 1:100, meaning that, in a sample taken from a biopsy, the amount of tumour cells is so small that a DNA analysis might give results from the tumour cell but might also give results from a healthy cell. In practice, this means that, tumour mutation tests need to be highly sensitive in order to detect mutations in a sample in which the majority of cells are not mutated. Therefore, an accurate mutation assessment requires specific techniques such as the ARMS® technology, licensed by AstraZeneca to the UK diagnostic company, DxS. This technology is based on the principles of a real-time Polymerase Chain Reaction (PCR), giving enough selectivity to detect 1 tumour cell among 100 healthy ones. If these detection technologies fail, further mutation analysis may not give valid results. For this reason, unless the tumour tissue is well identified, no further molecular analysis will give reliable results.

7.3.5 EGFR as a Prognostic Biomarker

EGFR mutations may also be used as a prognostic marker to assess the evolution of NSCLC, although this assumption remains more controversial and is still not very well documented (Lee, 2006). In a possible scenario, where prognosis is possible, technologies similar to those used in the case of diagnostics could be used to investigate how EGFR mutations or protein level analysis, may affect the remission of NSCLC.

7.5 Changing Clinical Practice

The emerging use of cancer biomarkers may produce a shift in the way physicians make treatment choices, which will eventually rely on the assessment of the individual characteristics of the patients and the genetic characteristics of their tumours. Until very recently, pneumologists considered that chemotherapy was the only treatment for advanced lung cancer; this is now changing thanks to the development of cytostatic

agents[12] and the emergence of targeted therapies based on major advances in the knowledge of tumour biology (Hansen, 2006). So, although there has, until now, been little interest from the NHS in prescribing drugs on the basis of EGFR testing, this may change in the future.

At the moment there are no clinical guidelines that recommend the use of a test that measures mutations on the EGFR gene because there is still not enough evidence of clinical utility and because Iressa® was never approved in the UK and Tarceva® is only recommended as second or third line therapy, when docetaxel is not an option. However, while in Europe EGFR testing is mainly used as an research use only (RUO) test, in other parts of the world such as Japan, EGFR diagnostics are being evaluated for future implementation in NSCLC drug treatment. In the future, and as further EGFR-related research results emerge, other countries may possibly consider the adoption of EGFR testing. This may encourage the UK system to use similar approaches or at least include them in the Health Technology Assessment Programme.

7.6 Genetics-Associated Business Options

EGFR testing in the future might offer the possibility of diagnosing whether there are mutations that predispose a patient to NSCLC and whether these mutations could be integrated into diagnostic products and drive drug use. However, as we have already seen, EGFR testing cannot yet be used as a confirmatory tool to assess drug response, because there is not yet a full understanding of the whole range of mutations that affect it. There is, therefore, a need to discover, not only which genes and which mutations are important for drug response, but also which gene-gene interactions underpin drug metabolism processes that could help to develop targeted diagnostic tests.

> *There is always a difference between what is possible (and there are lot of things that are possible) and then what you can actually demonstrate in an experiment or a clinical trial. And many things that are biologically very possible, if you put them to the test in the clinical study there is a huge number of additional variables, all which are important….the EGFR story is very possible, but what automately count is "can you show in a complex setting?" (respondent 16)*

[12] Cytostatic agents are those substances that are able to control the growth of cells, in this case the growth of tumours, instead of "killing" the tumour cells such as with chemotherapy.

In a situation where EGFR could be used clinically as a predictor of drug response, EGFR testing could help:

- AstraZeneca to find better biomarkers associated with the response to Iressa® in the Asian population and eventually translate some of this research into further sub-group analysis in Europe and the US in order to reach these markets (respondent 15);
- AstraZeneca find new biomarkers that improve drug efficacy in the European population and eventually reintroduce the drug into the European market;
- Roche implement the results of NICE's appraisal by undertaking further analyses in a sub-group population selected on the basis of EGFR mutations;
- Roche demonstrate that Tarceva® shows better efficacy and is more cost effective as a mono-therapeutic alternative to docetaxel.

7.6.1 Co-Developing Drugs and Tests

If it is finally proven that there is an improved clinical outcome after taking Iressa® or Tarceva® in patients with EGFR mutation-positive tumours, then it may be possible to consider the association of drug to test, which will imply a change in the drug label and a new license for the product. However, this would require new clinical trials to provide sufficient empirical results to meet the US Food and Drug Administration and the European Medicines Agency licensing procedures.

The co-development of drug and tests raises reliability concerns

> *I think maybe EGFR testing will help prescribing Iressa® or Tarceva® in the future, but we don't have enough information yet and we need to be careful that our policy isn't too restrictive because if we have a patient who is a non-smoker, who is female, has adenocarcinoma, has clinical characteristics that favour a response, but if that patient only has a few cells for analysis and they can't say "this patient definitely has EFGR gene amplification or mutation", it would be very frustrating to have to refuse that patient Tarceva®. So we need a flexible enough prescribing policy, we really need a wide prescribing policy that we can then exercise clinical judgement, design academic clinical trials, get funding from the research charities to run academic trials to work out who would get the drug and who would benefit most (respondent 21).*

Also, the co-development of drugs and tests raise issues of property rights, in particular if the companies involved in the diagnostic and the drug are different.

At the moment three companies have been involved in the launch of Tarceva®: OSI Pharmaceuticals, Genentech and Roche. These three companies are supporting studies designed to develop clinically validated diagnostic tests that may help oncologists to select patients appropriate for treatment with Tarceva®. The companies are also exploring the use of Tarceva® in a variety of solid tumour types and treatment regimens, including in combination with biologic therapies (Genentech, 2007).

In parallel to the activities of OSI Pharmaceuticals, Genentech and Roche, the diagnostic company Genzyme has developed two EGFR tests that identify NSCLC patients who are likely to respond to Tarceva® (and also Iressa®, although the drug being only commercially available in some countries). The first test detects an over-amplification of the EGFR gene and the second, a mutation assay, which detects the presence of EGFR mutations in patients with NSCLC (Genzyme, 2006). Genzyme has held, since 2005, the diagnostic rights to use these EGFR tests worldwide, although the tests were licensed to the British company DxS firstly for use all over the world with the exception of the US, Canada, Mexico and Hong-Kong and, since 2009, also in these countries.

At the same time, DxS, which was founded in 2001 by ex-AstraZeneca managers, provides different types of EGFR mutation analysis services (Little, 2005). Among these, it offers testing services for 25 different mutations in the tyrosine-kinase domain of the EGFR gene, for which it uses the ARMS® technology (Amplification Refractory Mutation System) technology licensed from AstraZeneca. This technology is targeted at identifying SNPs as well as other DNA mutations.

Therefore, despite the lack of clinical utility data on EGFR testing, the reality is that companies are investing in developing EGFR diagnostic tools. One of the main questions herein is whether the commercialisation of EGFR tests will, in the future, lead to the co-development of EGFR tests together with Iressa® and Tarceva® so that Iressa® can reach the European and US markets and the use of Tarceva® in the UK will broaden from a second/third line therapy to a first line therapy. The second question that stems from the previous one is which company will be behind the drug-test co-development. This question cannot yet be answered, although there are important points to consider:

- Genentech is a world diagnostic leader. At the same time it is owned by Roche, the manufacturer of Tarceva®. These two conditions turn Genentech into a strong candidate for potential drug-test co-development (respondents 16 & 19).

- At the same time as Genentech could be interested in EGFR testing in the future, DxS also has a strong visibility in the lung cancer market as it offers different types of diagnostic EGFR testing services.

7.7 New Business Models

The integration of diagnostics with treatments represents a great opportunity for business, in creating new alliances and maximising the value of a combined product (Arnold and Hall, 2005). One of the objectives that a diagnostic company pursues is to attract interest in and demand for their diagnostic tools and/or services by clinicians. However, in the UK, diagnostic companies are not qualified to sell their products directly to the clinicians. They are obliged to do it through hospital intermediaries, mainly hospital laboratories, who have the accreditation to provide diagnostic services within the hospital.

The business model of a diagnostic company follows two paths:

- Diagnostic companies can sell their products to other businesses, for example other pharmaceutical companies that need diagnostic tools during the drug development process, especially when it becomes necessary to screen the suitable participants that enter a clinical trial. This is the case with the Affymetrix P450 gene chip. The device measures mutations in the genes that code for the cytochrome P450, a protein which intervenes in the liver metabolism of many drugs. Mutations in any of the genes that codify for the cytochrome can result in a malfunction in the liver metabolism of a drug and can cause adverse drug reactions.
- Diagnostic companies can sell their products or services to other clinical intermediary laboratories. Doctors working in the public sector in the UK will accept a diagnostic test provided by these clinical laboratories if it is reimbursed by the NHS, but will have more difficulty accepting a test that is not reimbursed. Normally if a test is reimbursed it means that it has been widely accepted and is considered good practice and most probably its use is also recommended by NICE.

However, when a test is not reimbursed by the NHS it will be risky for the clinician to prescribe it and s/he will only be able to do so as long as the budget of his/her particular Trust enables him/her to do so. In the private sector, where treatments are paid for by individual patients, it is more likely that diagnostics are more easily introduced. But,

The fact that diagnostic companies in the UK can only sell their diagnostic kits to other research or clinical laboratories restricts their margin of operation (in other countries, such as the US, tests can be sold directly to clinicians).

However, diagnostic companies have developed strong mechanisms for promoting their tests. Promotion is mainly done by key opinion leaders, who spread knowledge about diagnostic tests through their publications. These opinion leaders are prestigious research institutes, research groups, or even expert individual researchers whose views influence the opinions of and demand from other clinicians.

In the case of EGFR the key opinion leaders were the laboratories in Boston who first discovered the possible relationship between EGFR and the response to TK inhibitors. So, often, diagnostic business models rely on opinion leaders to reach a particular market.

7.8 Harmonisation of Cancer Research and Patient Demand

The importance of investigating new ways of treating NSCLC relies on the fact that its prognosis is very poor and only 2% of individuals survive after five years (Roy Castle Lung Cancer Foundation, 2007). This leads to a need for more research in the lung cancer area (NCRI, 2006). However, despite the fact that lung cancer is at the top of the list of causes of deaths in oncology, it only receives 3% of the cancer research funding made available by the government and cancer charities. By contrast, leukaemia research receives 17% of that budget (Roy Castle Lung Cancer Foundation and Cancerbackup). Some of the underpinning reasons for the lack of funding for lung cancer research may be the following (NCRI, 2006; Hansen, 2005):

- It could be thought that lung cancer research will be unrewarding because it is considered unlikely to have a major impact on patient outcomes.
- Since lung cancer survival is poor, there are fewer patients able to take on an advocacy role than there are for other common diseases such as breast cancer and so the pressure of such groups is smaller than in other areas where there are more survivors (respondents 18, 21 & 26).
- With the exception of the Roy Castle Lung Cancer Foundation, there are no major national charities devoted to lung cancer, unlike for breast or prostate cancer.

- Lung cancer is a stigmatised disease due to its relationship to smoking (only one in eight people who are diagnosed with lung cancer have never smoked). This might foster a culture of 'blame' and might be one important reason for not promoting lung cancer research, as it could be avoided in a large number of cases (UKLCC). However, lung cancer patients are not denied treatment due to smoking and it could be argued that, because lung cancer develops at later stages in life than breast cancer, for example, these patients have contributed with their taxes for longer periods of time and may have certain "privileges" regarding the availability of treatment. It could also be argued that smoking also influences cardiac diseases and the level of stigmatisation for these patients is less (respondent 21).

7.8.1 Research Organisations

In the last few years, the acknowledgement that lung cancer research in the UK was weak has pushed the introduction of multi-disciplinary teams, who have significantly improved the treatment of patients and increased the number of trials on offer, giving patients a greater choice of treatment options. A series of associations and non-profit organisations have been created:

- The UK Lung Cancer Coalition (UKLCC)[13], launched in November 2005, is a partnership of clinicians, charities and health care companies which has been formed to raise the profile of lung cancer, particularly among MPs. It is the nation's largest multi-interest group for lung cancer. The long-term aim of the coalition is to help co-ordinate efforts to improve lung cancer survival rates.
- The National Cancer Research Network (NCRN)[14] was also created in response to the need to improve the infrastructure within the NHS for clinical research into cancer, and to ensure that research is better integrated with cancer care, as outlined in the 2000 Report of the Science and Technology Committee on Cancer Research. The National Cancer Research Network has 33 centres all over the country, providing the NHS with the infrastructure to support clinical cancer trials in the UK.
- One of the main obstacles to lung cancer research is the lack of samples from tumours. Up until now, only three UK cancer research centres have held lung cancer

13 http://www.uklcc.org.uk/

14 http://www.ncrn.org.uk/

samples, and these were only accessible to the researchers working within these centres. To overcome this, some partners of the National Cancer Research Institute (NCRI) have created **OnCore UK**[15], a national bio specimen and information resource for cancer research, which began on a pilot basis in 2006. OnCore will collect samples of tumours and blood donated by patients participating in clinical trials within the National Cancer Research Network (NCRN).

- The National Cancer Research Institute[16] is an organisation formed by companies, public institutions and charities working in cancer research. Its mission is to provide funding and support for cancer research databases, research initiatives, clinical trials and research facilities.

7.8.2 Patient Groups

The Roy Castle Lung Cancer Foundation is one the main UK non-profit organisations dedicated to giving support to lung cancer patients. Other patient organisations such as Cancerbackup are also involved in providing support to lung cancer patients, although the Roy Castle Lung Cancer Foundation is exclusively focused on lung diseases, its behavioural component (smoking) and its associated problems. The role of the Roy Castle Lung Cancer Foundation is crucial in providing support to lung cancer patients, in particular since the disease is heavily associated with smoking. Through its network, it provides information and support to the 40,000 people throughout the UK who are diagnosed with lung cancer each year. The foundation is also actively involved in programmes of smoking cessation and research. They are also involved in the coordination of a major European study into early lung cancer[17]. But the major research project is the Liverpool Lung Project (LLP), a ten year population-based study aimed at developing a molecular-epidemiological risk-assessment model, based on smoking, environmental exposures and genetic susceptibility. At present, there is no such model, and the results will be of great value in understanding the aetiology of lung cancer, in selecting high-risk individuals for prevention studies and in forming hypotheses for surveillance interventions.

15 http://www.oncoreuk.org

[16] http://www.ncri.org.uk/

[17] http://www.euelc.com

The potential impact of this research is the identification of individuals who are at risk of developing lung cancer and the provision of intervention measures. Currently, the importance of this lies in economic dictates that mean that screening for lung cancer will not be available for an entire population[18]. Consequently, there is a need to identify those people at highest risk who could benefit from prevention measures.

At the moment, the Roy Castle Lung Cancer Foundation and the Wolfson Institute of Preventive Medicine have presented outlined plans for a lung cancer screening trial of 14,000 people, which they believe could provide better answers for lung cancer treatments by 2013.

7.9 Summary

EGFR testing: the potential to improve drug response to Iressa® and Tarceva®

Lung cancer is the most common cancer in the world and the first UK cancer killer, with 37,000 new patients in the UK every year (Roy Castle Lung Cancer Foundation, 2007). There are different types of lung cancer, although this case study will only focus in non-small cell lung cancer (NSCLC). Treatments given to patients upon diagnosis vary. First line therapy refers to the first treatment given to the patient after it has been diagnosed whether it is localised in the lungs or metastasic and spread in the lungs and/or other parts of the body. Second and third line therapies apply to patients who have failed the first and second line treatments consecutively. NSCLC can be treated with surgery, chemotherapy, radiotherapy or a combination of these, depending on the stage of the cancer when it is diagnosed (Cancer Research UK, 2008). Some drugs like docetaxel (Taxotere®: Sanofi-Aventis) are also prescribed a second or third line treatments. However, despite the available treatments, lung cancer is still a fatal disease with survival average of only six months (Roy Castle Lung Cancer Foundation, 2007)

In the period between 2003 and 2005, two innovative therapies emerged. AstraZeneca developed Iressa® and Roche Tarceva®. Both drugs were very similar although in the UK only Tarceva® reached the market. Iressa® was never approved due to problems in demonstrating improvement in survival during clinical trials. Nevertheless, both Iressa® and Tarceva® were approved in Japan and other Asian countries. These drugs represented a new challenge for the treatment of NSCLC cancer. They were classified as biologic drugs (a new generation of drugs made from a living organism or its products that are often used to treat different types of cancer) and promised considerable improvements in the survival rates of NSCLC sufferers. Additionally, unlike other NSCLC treatments, they did not require hospitalisation as they were delivered as oral tablets.

When Tarceva® was approved in Europe in 2005, the National Institute of Clinical Excellence (NICE), responsible for monitoring the use of drugs and devices across the NHS launched a technology appraisal to examine whether the drug should be reimbursed by the NHS. In March

[18] The Liverpool Lung Project; Research Protocol. May 2005

2007, an appraisal determination, recommended Tarceva® in patients suffering from NSCLC, but only as a second line treatment and when docetaxel was not an option (NICE, February 2007). These guidelines on Tarceva® were highly contested and faced the opposition of the manufacturer (Roche, 2007); the main lung cancer patient groups; the Roy Castle Lung Cancer Foundation as well as Cancerbackup (Roy Castle Lung Cancer Foundation and Cancerbackup, 2007b), the Royal College of Physicians (Royal College of Physicians, 2007), and the British Thoracic Society (British Thoracic Society, 2007). But nevertheless, the final technology appraisal came out in September 2008 and NICE did not retract its previous statement and still recommended the use of Tarceva® as a second line therapy when docetaxel was not an option, suggesting Roche to do further sub-group analysis that demonstrates superiority of Tarceva® over docetaxel (NICE, 2008b). At the moment both AstraZeneca and Roche are doing research in Japan, where they have a bigger market and where there seems to be a better response to the drugs among NSCLC patients. However, it is expected (although the particularities of the business strategies that both Roche and AstraZeneca plan are not fully known) that both companies will aim to widen their drug market.

In the UK, clinicians in the NHS now need to implement Tarceva® as NICE suggests: as third line therapy when doceaxel is not an option, although it could be possible that they may also want to implement Tarceva® locally for never smokers, who are a patient population that seems to respond favourably to the drug. In the meantime, Tarceva® is still being tested in clinical trials in the UK. Cancer Research UK is funding a phase 3 trial, the TOPICAL study (Tarceva® or Placebo In Clinically Advanced Lung cancer). Recent publications advocate Iressa® to be as effective as chemotherapy (ScienceDaily 2008), a statement that may be influential in the future use of Iressa® worldwide. In fact, following these events, in November 2008 NICE announce a new appraisal on Iressa® (NICE 2008). NICE aimed to evaluate the cost-effectiveness of the drug in the treatment of NSCLC. The first results of this appraisal are expected to appear in May 2009, after all the technical data has been gathered and this, again, may change the current regulatory regimes that control service delivery in NSCLC in the UK.

The pharmacogenetic properties of Iressa® and Tarceva® was not found after they were approved. They are both tyrosine-kinase inhibitors, as they block the tyrosine-kinase activity of a cell protein, the EGFR (Epidermal Growth Factor Receptor), which seems to be involved in the development of the NSCLC (Herbst and Kies, 2002, Wakeling et al., 2002, Comis, 2005). Therefore, there appears to be a correlation between EGFR mutations and drug response, although these mutations do not always explain why some patients respond better than others (Lee, 2006). Current knowledge informs that, although there are more than 20 known mutations associated to the EGFR gene, it is not clear which ones affect response to Iressa® and/or Tarceva®. Also, not only gene mutations but gene amplifications can affect drug response, but there are no clear patterns that explain it. However, despite the existing technological uncertainties around EGFR mutations/amplifications and drug response, it can be anticipated that, if current research gives light on a strong drug-gene association, in the future Iressa® and Tarceva® could be co-developed with a genetic test, which may be an opportunity for Iressa® to reach the European and American market and, for Tarceva®, to widen its indications in Europe.

Chapter 8 . PGx Controversies and Future Options for Service Delivery

8.1 The Socio-Technical Network: from Drug Development to Service Delivery

The following sections are structured to promote an understanding of how the existing controversies and future uncertainties around TPMT and EGFR testing are articulated by the main actors involved in drug development (e.g. researchers, pharmaceutical and biotechnology companies) and service delivery (e.g. NHS Trusts, Clinicians), with a particular focus on the regulatory processes that control these mechanisms, highlighting the existing regulatory gaps and conflicting elements that hamper the widespread adoption of PGx in the clinic. The chapter will start by identifying the critical points that hamper the use of PGx. Then, the discussion will build around three main themes: the current impact of PGx on drug development, the regulatory processes and existing gaps that rule the development and use of medical technologies, to finish by describing existing PGx mechanisms of service delivery, as well as future options. The chapter will finish with a country comparison between TPMT testing services in the UK and Spain and how institutional frameworks affect these.

8.1.1 Identifying the origins of the problem

When we talk about PGx, there is a mismatch between what some opinion leaders from pharmaceutical and biotechnology companies anticipate may happen and what happens in reality in clinical practice. This gap between expectations and reality represents the existing needs, problems and barriers that PGx would need to overcome, in order to deliver a public health service.

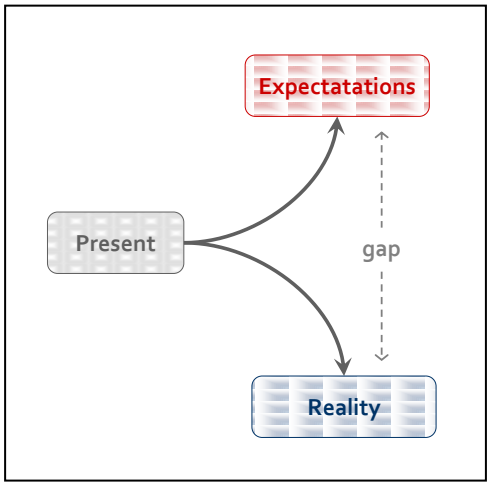

Figure 8.1 : gap between expectations and reality (Loveridge, 2001)

This gap between expectations and reality (illustrated in fig 8.1) is the result of a strategy, often used to introduce new products and processes into the market. Innovators generate images of the future that reflect the high expectations they put on their products. These expectations link the social with the technical and create a future world according to what innovators expect the impact of their technologies is likely to be.

For example, when pharmaceutical companies develop a new drug, they automatically define the diseases their drug will target; the patient population eligible to take that drug; how those patients are going to benefit and how the health care system is going to benefit. By doing this, they are creating a world that defines specific uses of the invention in the context of a desired market.

In the case of PGx, the anticipated benefits and the possibility of delivering more personalised therapies (Collins, 2003, Venter et al., 2001) have contrasted with the very few existing clinical applications (Royal Society, 2005).

8.1.2 Critical Points

PGx has been defined to follow two technological trajectories: the first one aimed at preventing ADRs and, the second, at improving drug response (Hedgecoe and Martin, 2003). Even though they are different, they share common characteristics. They both need diagnostic testing to assess how genetic mutations affect drug response and how these could be used to avoid ADRs and improve the patients' response to drugs. Therefore, all the actors involved in these processes need to understand how diagnostic testing is going to impact on them and how it is going to be used in clinical practice. Hence, diagnostic testing here constitutes a critical point in the adoption of PGx.

The way in which diagnostic testing may be used in clinical practice will affect drug and biotechnology companies who might need to shift their drug development strategies towards the co-development of drugs together with diagnostic tests. This will require a better integration of biomarkers research into drug development strategies. Diagnostic testing will also need specific regulations and this will impact on the existing drug regulatory system. Clinicians and pharmacists will need to follow new protocols that integrate diagnostic testing and drug prescription as well as new ways of being treated. Drugs withdrawn from the market may see in diagnostic testing an opportunity to narrow their target population and achieve market approval, and post-marketing drug surveillance

mechanisms may also need to be adapted to allow for the influence of diagnostic testing over drug response.

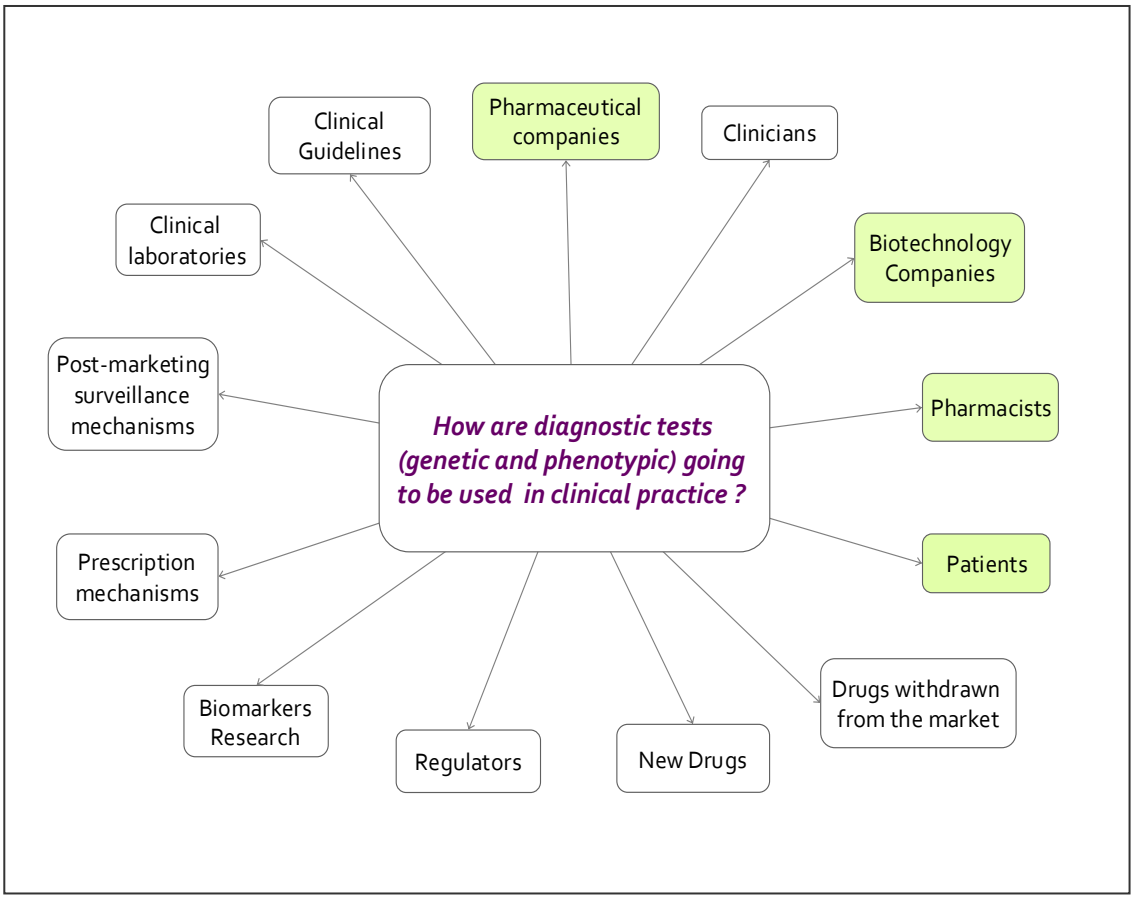

Figure 8.2: Diagnostic testing as a critical point for introducing PGx in clinical practice.

So, if pharmaceutical and biotechnology companies aim to develop new drugs and tests, if regulators aim to establish adequate frameworks to approve these drugs, if clinicians aim to offer better treatments and if patients want to benefit from better drugs, then, they all need to understand the principles of diagnostic testing. For thesereasons we conclude that diagnostic testing is a critical point for the implementation of PGx both in drug development and in service delivery, although the objectives that each of the actors follow are different (see figure 8.3):

- Pharmaceutical and biotechnology companies use PGx to develop new drugs, new tests and/or both, or to target existing drugs to specific sub-populations. New drugs may see an improvement in therapeutic response if they are targeted to a specific patient sub-population. Drugs withdrawn from the market might be introduced in the clinical setting if an association between genetic biomarkers and drug response

is established so that the drug can be targeted to a population with a particular genetic/phenotypic profile (and not to the overall population). Biomarkers research will provide the scientific knowledge about the genetic origins of drug response and contribute to improvements in drug prescription.

- Regulatory agencies will need to adapt to the needs of PGx and will need to provide legal coverage for the use of new drugs in association with diagnostic tests. Then, the existing post-marketing surveillance mechanisms will also need to assess the unexpected impacts of drugs in accordance with how patients are pre-screened for personalised drugs.
- Clinicians may also need to adapt to the requirements of personalised therapies, following new testing procedures and clinical guidelines that comply with good clinical practice standards. Clinical guidelines, at the same time, will need to include the testing needs associated with the use of personalised medicines. Pharmacists, at the same time will need to consider results from diagnostic testing in order to fine-tune the prescription of drugs, in terms of both chemical components and doses.
- Clinical laboratories will expand their services to PGx and this will require new expertise in the area of PGx, as well as testing facilities suited for the purpose.
- Finally, patients will seek to benefit from the use of a more personalised approach to health care.

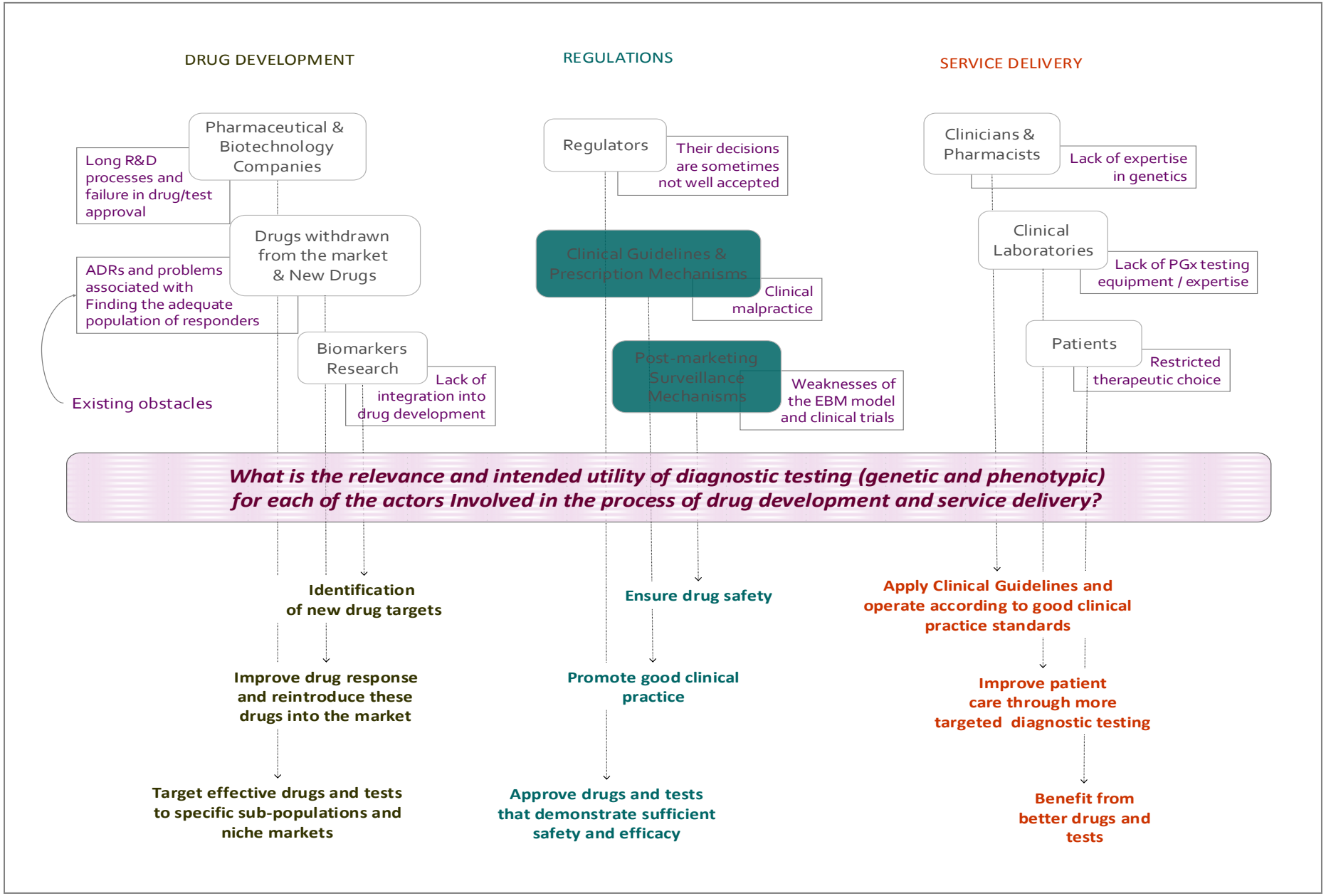

Figure 8.3 : representation of the obstacles that the different actors involved in drug development and service delivery find, as well as the opportunities that PGx offers to overcome these obstacles.

8.2 Drug Development

Chapters five, six and seven presented a detailed explanation of what TPMT and EGFR testing are. These chapters highlighted the scientific and technological aspects that will, later on affect PGx implementation policies. As we saw in those chapters and, as we, earlier on introduced, there are substantial differences between TPMT and EGFR testing in the UK: while TPMT testing aims to prevent ADRs caused by an off-patent drug, EGFR testing aims to improve the response to two drugs under development. Some of the differences in using PGx for an old drug and for a new drug are that, usually, there is no private incentive for investing in PGx for old drugs and therefore, there is likely to be no major impact in terms of drug development. On the other hand, PGx is likely to have more impact on the development of drugs for NSCLC, as we pointed out in chapter six. For this reason, the section on drug development is going to focus on the potential impact that EGFR testing might have for widening the indications of Tarceva and for re-introducing Iressa® into the UK market.

In the UK, there are no private incentives to use TPMT testing to improve the use of AZA or 6-MP. This does not mean that these incentives do not exist elsewhere. In the US, the company *Prometheus*, has been offering TPMT testing for several years. In Spain, as we will see at the end of this chapter, the company who was commercialising AZA, started offering TPMT testing as part of a strategy that aimed to co-develop the drug and the test so that the dosage of AZA could be increased in those individuals who had normal levels of TPMT (90% among the population). This is partly the consequence of a health system in which regulations are much less stringent than those of the UK. However, the comparison of both systems will not take place here but in section 8.6

8.2.1 In Search of a model of Clinical Utility of EGFR Testing

The differences in approval of Iressa® and Tarceva® among different countries have posed several dilemmas concerning the safety and efficacy of these drugs. Similarly, the possibility of using biomarkers of drug response to prescribe these drugs is still highly contested. These, as well as other controversies will be further explained in the following sections.

Iressa® was never approved in the UK but was approved in Asian countries such as Japan, on the basis that Asian patients respond better to the drug. This was facilitated by the fact that Japan has a fast track drug approval system. Tarceva®, on the other hand, was approved in both the UK and Japan, although the Japanese Health Service allowed a broader use of the drug than the NHS did (respondents 16 & 18). In the UK, NICE's final appraisal concluded that Tarceva® should be used as a second or third line treatment, based on the data submitted by the manufacturer and later consultations with different professional bodies.

The variations in the use of Tarceva® in the UK and Japan, illustrate the globalised nature of R&D and the local application of regulations.

Regulations rely on evidence, among other factors. The controversy arises when it comes to defining what should be understood as "good enough" evidence and how this is used to introduce a new drug into a local market.

8.2.2 Re-Introduction of Iressa®: Searching market strategies

Iressa®, like Tarceva®, is a tyrosine-kinase inhibitor. Both drugs are very similar, although Iressa®, just before reaching the market in 2004, had some results that did not support an improvement in life survival and, as a result, was rejected in the European and US approval processes (it was only used on a compassionate basis for those patients who had already entered clinical trials). However, Iressa® reached the market in Japan. As was discussed in chapter seven, two factors facilitated this: firstly, similarly to the situation with Tarceva®, the Asian population were better respondents; secondly, Japan has a fast track drug approval system that enabled the process. However, despite the successful approval of Iressa® in Japan and even assuming that any drug would aim to reach the European and US markets, it is uncertain which strategies AstraZeneca (the manufacturer of Iressa®) would focus on in order to reach this aim.

- It is unclear whether AstraZeneca would be looking at a possible EGFR test-drug co-development. If so, it is also unclear who would develop the test, since AstraZeneca (unlike Roche) is not involved in diagnostic technologies.
- It is unclear what the impact of clinical opinion will be, in a hypothetical future situation where Iressa® was introduced in the UK, since, at the moment, there is a clinical tendency to say that both Iressa® and Tarceva® are very similar drugs.

8.2.3 Tarceva®: looking for adequate patient sub-populations

After Tarceva® was approved in Europe in 2005 for treating NSCLC, it was found that mutations on the EGFR gene could influence drug response. At the same time, it was also found that patients who suffered from adenocarcinoma, who were of Asian ethnicity, who were female and who had never smoked, were also better responders to Tarceva® than the rest of the population. However, even when this data is available and, despite some diagnostic companies already offering kits for EGFR analysis, the use of Tarceva® in the UK has not been influenced by either of these factors. The manufacturer simply was not able to justify the clinical relevance of using genetic (i.e. having mutations on the EGFR gene) or phenotypic (i.e. having NSCLC adenocarcinoma, being Asian, female, and never –having smoked) analysis to predict drug response.

NICE's final technology appraisal concluded that Tarceva® should only be reimbursed in the NHS for patients suffering from NSCLC as a second or third line treatment, when there was no better option. Nevertheless, NICE suggested to Roche (the manufacturer of Tarceva®) that further sub-group analysis should be carried out. The question now is, which type of sub-group analysis Roche is focusing on.

- At present, Roche is doing research on Tarceva® in Asian countries (including Japan and Singapore), because the drug has a higher demand in these countries, where patients respond better than in Europe (probably due to certain genetic determinants of Asian ethnicity, still not well understood, that influence drug response). However, how the results of this research will be translated into the European context is unknown.
- It is uncertain whether Roche is willing to study the response of Tarceva® in sub-groups according to phenotypic traits (such as being Asian, female and never having smoked) or genetic traits (EGFR positive). In fact, no clinical drug-test association has been found yet. Nevertheless, it should be highlighted that Roche has been granted rights of exploitation of the EGFR29 mutation kit, developed by DxS. So, despite the fact that Roche has not found conclusive proof associating EGFR mutations to drug response, the fact that it has a license to commercialise the EGFR29 mutation kit, reveals that there is some interest in genetics. It should also be noted that mutations on EGFR also intervene in drug response to other diseases, such as pancreatic or colorectal cancer. The fact that Roche is granted a

license to use the EGFR29 mutation kit should not be used to make conclusive remarks on its future influence over Tarceva®.

- In the UK and as it appeared in the mini-questionnaire we circulated among clinical oncologists, some clinicians were in favour of using Tarceva® in NSCLC patients who have never smoked. The clinical experience of these clinicians gives a positive advantage to Tarceva® than to existing treatments. However, no statistical data has confirmed this yet. Nevertheless, some NHS Trusts, in some cases, offer Tarceva® to these patients as it has shown to increase survival in several months and even years (respondents 21 & 26). The opinions of these clinicians, as it happened in the case of TPMT testing, are a strong driver for technology adoption, even in the case where the technology has not been evaluated fully in those specific situations.
- It is uncertain whether NICE will change their final appraisal of Tarceva® and reimburse the drug in never-smokers, because of the evidence provided by clinicians.

8.3 Regulatory Factors that affect Drug Development and Drive Service Delivery

As we have noted in chapter four, regulations affect both the development of drugs and their delivery. The set up of new regulatory regimes depends on the institutional setting where a particular drug is being marketed and the health system where it is delivered. However, these regulations are often set up once the technology has emerged, requiring a period of adaptation during which a number of gaps need to be overcome. This has been the case for PGx. The lack of consistent regulations that control the access to TPMT and EGFR testing has created "informal"[19] mechanisms of service delivery. This chapter aims to give some light into how these "informal" mechanisms have been created, to suggest ways of overcoming the existing weaknesses of the regulatory/delivery system.

[19] The term informal here refers to differences in technology adoption across the country due to a lack of a systematic way of implementing these in clinical practice.

8.3.1 Assessing Clinical Utility

Clinical Trials are the existing mechanism to assess the safety and efficacy of new drugs in the market. Clinical trials, together with the results from cost-effectiveness studies give an idea on whether a treatment reaches enough clinical utility.

Clinical trials are done on a sample population that is taken as a representation of the overall population and, despite the weaknesses that this implies, the result of clinical trials is, at the moment, the required tool to introduce new drugs into the market (although not necessarily into the health system as we will see later).

One of the major problems that PGx faces at the moment is the lack of sufficient results of clinical trials, which leads to a gap in the understanding of how genetic/phenotypic profiles affect drug response. This, together with insufficient cost-effectiveness studies, creates a disincentive for implementing PGx in the clinic, as there is not enough proof of clinical utility to support its use (respondents 12, 13, 14 22 & 25) (the definition of clinical utility is provided in section 3.3.1).

In the light of the weaknesses associated with the insufficient proof of clinical utility of PGx applications, in the UK, the DoH funded the TARGET study, the first randomised controlled trial of a PGx test in the NHS (results of which are not yet publicly available), aimed at looking at the benefits and cost-effectiveness of doing TPMT genotyping instead of phenotyping (NOWGEN, 2009).

The results of the TARGET Study may inform the DoH on the suitability of TPMT pre-screening before prescribing AZA. However, the fact that TPMT testing has not yet been widely implemented does not exclusively rely in the lack of quantitative studies. Even when those studies are available there are discrepancies on their validity and reliability.

8.3.1.1 The Contested Economics of TPMT Phenotypic Analysis

In Chapter 5 (Section 5.13) we presented some economic data in relation to he cost of TPMT testing and the cost of an ADR (Gurwitz et al., 2009, Compagni et al., 2008, Graham et al., 2004, Payne et al., 2009). These economics are contested.

Claims against the use of TPMT phenotyping argue that, in order to find a person who has no or very low TPMT levels, 300 people would need to be tested. The cost of this would be,

approximately £8,100, if we consider £27 to be the average cost of a TPMT test. Followers of this argument claim that this is too expensive, if we take into account that patients experiencing ADRs after taking AZA or 6-MP could be picked up very quickly without the need of a TPMT test, since these patients are monitored for white cells and liver function tests on a daily (for ALL) or weekly basis (for the rest of autoimmune conditions for which AZA is prescribed) (respondent 24).

Contrary opinions, on the other hand, argue that blood count tests are a poor indicator of azathioprine intolerance in some (a small number of) patients, who respond to the drug in an idiosyncratic manner (respondent 1), and therefore TPMT testing would be beneficial. These patients are almost totally deficient in TPMT and accumulate extremely high levels of 6-TGNs (the origin of ADRs) (see sections 5.1 and 5.2). The accumulation of TGNs occurs many days before the bone marrow reserve is exhausted and the blood count begins to fall, so, even when the ADR cannot yet be diagnosed, the blood cells might be dropping and, at this stage, it would be very difficult to treat the adverse event because the patient may already be seriously ill (Anstey et al., 2004). So, the economic impact of TPMT testing needs to be evaluated in the context of, not only the cost of testing patients, but also the cost saved by avoiding ADRs. A recent review supports this claim by saying that the TPMT enzyme test is cost-effective (Payne et al., 2009).

According to two interviewees, the major benefit of the centralisation of TPMT testing was the optimisation is costs. Each TPMT reference laboratory analyses between 11,000 and 12,000 samples every year, at an average price of £27/sample, means a revenue of almost £300,000. According to these respondents, this would outweigh the costs of setting up a laboratory infrastructure (estimated at £6,000 a year in infrastructure alone and between £12,000 and £15,000 a year once the laboratory starts screening) and therefore would make TPMT testing worthwhile (respondent 1 & 22).

However, despite the available economic data, the use of TPMT testing in the UK is only systematic in dermatology, and not in any other clinical specialties because, even though there is evidence of benefits (Graham et al., 2004, Ford et al., 2004b, Compagni et al., 2008), there are no robust utility studies (respondent 13). There have not been any conclusive clinical trials that state that TPMT testing is more beneficial than other ways of testing and, in this context, the TARGET Study (that is assessing the cost-effectiveness of phenotyping vs. genotyping) is the first attempt to do so.

In ALL, the entire situation is different because TPMT testing is part of the protocol of the UK ALL 2003 trial, a clinical trial that is aimed at looking for optimal therapies for treating ALL and which includes all children with ALL. Therefore, regardless of clinical opinion or economic data, TPMT testing is done as part of the trial on a regular basis. Nevertheless, some clinical oncologists who treat ALL patients do not agree about the benefits of TPMT testing for ALL, because, at the moment it is not a substitute for routine blood monitoring, liver function tests and electrolyte tests, and some clinicians argue that routine blood monitoring would also detect a slow TPMT metaboliser very quickly (respondent 24). Other clinical oncologists, on the other hand, support the use of TPMT testing, claiming that it would be beneficial as it would detect these slow metabolisers before they take 6-MP (respondent 27).

As was pointed out in Chapter 5, it seems therefore that, although the existing cost-effectiveness studies highlight the benefits of TPMT testing, this is not enough for TPMT adoption, because:

- The economic considerations of TPMT testing are still limited by the under-reporting of ADRs due to a lack of robust systems for tracking them. In the UK, reporting ADRs on the Yellow Card Scheme is done on a voluntary basis. It is, therefore, necessary that pharmacovigilance strategies are implemented to enhance ADR reporting and make data available, not only for clinical safety purposes, but also as the basis for economic studies (Compagni et al., 2008).
- There is a lack of well-designed prospective studies in which the costs of ADRs have been systematically collected and evaluated. Improving existing economic models will help achieve this aim and could better support the implementation of PGx (Payne et al., 2009).

8.3.1.2 The Economics of TPMT Genetic Analysis

Besides the ongoing TARGET study and, despite the few PGx clinical trials, there are some studies that have focused on analysing the cost-benefit of TPMT genetic analysis. One of these analysed the effect of genotyping in inflammatory bowel disease, concluding that the use of pre-treatment screening for TPMT polymorphisms in IBD patients commencing azathioprine therapy, represents good value for money, with a pre-treatment genotyping

cost of £347 per life-year saved or QALY[20] for a 30 year old and £817 per life-year saved for a 60 year old. These figures compared favourably with other health care technologies (Winter et al., 2004). Another cost-effectiveness study carried out in four European countries (Germany, Ireland, the Netherlands and the UK) that evaluated TPMT genotyping in Acute Lymphoblastic Leukaemia (ALL), concluded that TPMT genotyping in these patients also showed favourable cost-effectiveness (€2,100 per life-year gained) (Van den Akker-van Marle et al., 2006). Nevertheless, the use of TPMT genetic analysis is very low, much lower than the use of the phenotypic test.

8.3.2 NICE and the NHS Reimbursement Policies

The introduction of new technologies into the NHS is driven by an assessment of their health benefits in the context of a market mechanism that provides and pays for treatments according to clinical utility and cost-effectiveness. For the NHS, clinical utility (and cost-effectiveness in particular) is the rationale for technology adoption. However, this does not mean that the cheapest treatments are reimbursed exclusively. For instance, biologicals like anti-TNF drugs, which cost an average of £9,000 a year, have been approved by NICE and are widely used in the NHS. Other drugs, for example some generics (such as AZA), have not been appraised by NICE but have been in the market for a long time (they came into the market long before NICE was created) and are widely used.

Therefore, cost-effectiveness becomes a critical issue when there is a very expensive drug that works well. In these circumstances, it is difficult to justify that high cost, while for most cheap medications cost-effectiveness is not an issue (respondent 22).

8.3.2.1 Clinical Implementation without NICE Technology Appraisal

Treatments with AZA are reimbursed by the NHS, because the drug is cheap (£20 a month, approximately). TPMT testing, on the other hand, which costs £27 per patient, is not reimbursed nationally (only locally) because NICE has not appraised it and, often, without a "stamp" of approval that assures clinical utility, it is difficult for the NHS to reimburse the test.

[20] "£ per life-year saved" refers to the reasonable quality of life a person might gain as a result of treatment.

Without this "stamp", the NHS is reluctant to pay for something that they do not think will have an impact on cost or patient care, despite the benefits claimed by some clinicians, the TPMT reference laboratories and some of the published literature (respondent 14).

However, although NICE is the formal mechanism for reimbursement in the NHS, when NICE does not give an opinion about a particular drug or a treatment, there is some freedom for NHS Trusts, who can manage some of their own budget independently, to decide which of the treatments to implement. For instance, there are some biological treatments called B-cell depleting therapies, which cost around £6,000 a year, from which patients with Lupus erythematosus (a systemic autoimmune disease that affects different organs) can benefit. Some Trusts have decided that they can afford an expensive treatment needed in only a very restricted number of patients (respondent 22). Similarly, some NHS Trusts have decided to reimburse and implement the use of TPMT testing, although not all the NHS Trusts have done it. This is an indication that the evidence used to make decisions as to whether or not to reimburse technologies at a Trust level is not very clear (respondent 14) and technology adoption at a local level is more a matter of willingness to pay.

In the light of the unwillingness of most the NHS to reimburse TPMT testing, the reference laboratories, as well as some groups of clinicians such as the dermatologists, claim that the test is not expensive and that the benefits are large, not only for patients who have low or no TPMT response and who should not be taking the drug, but also for people with intermediate levels, who could benefit from a reduction in the azathioprine dose.

8.3.2.2 Partial Implementation: Tarceva® Technology Appraisal

NICE concluded in the final Tarceva® appraisal determination that the drug could be used under limited circumstances, favouring the use of docetaxel (an existing drug that was already used in the treatment of NSCLC) against Tarceva®. This decision was highly contested and faced opposition from several professional bodies and patient associations: the British Thoracic Society, the Association of Cancer Physicians, the Royal College of Physicians, the Roy Castle Lung Cancer Foundation, CancerBackup and Roche. Their main claims were the following:

- Tarceva® is a promising drug because currently there are no better alternatives for NSCLC patients. Tarceva® does not only improve survival rates but also quality of life.

- Unlike other cancer treatments, Tarceva® is delivered in tablets and does not require hospitalisation, it also prevents serious ADRs that docetaxel cannot.
- There is no direct data that compares the effectiveness of Tarceva® against docetaxel; there are only indirect relationships taken from different clinical trials.

So, firstly, Tarceva® will need to demonstrate better performance than docetaxel and afterwards, the adoption of the drug will depend on user experience and on how some clinicians spread information about its benefits and encourage others to use it, a process which is likely to take a long time as it requires social learning.

8.4 Service Delivery

Section 8.2 was limited to the analysis of the implications of EGFR testing for drug development and not service delivery, because EGFR testing was exclusively used as a drug development strategy in the UK. In this section we will widely discuss the implications of TPMT testing for service delivery. We will, however, not refer to EGFR testing since it has not reached the clinic yet. At the moment EGFR testing is being used exclusively as a research strategy.

8.4.1 TPMT Testing: Reference Service

While TPMT testing is not formally recommended by NICE and the test is not compulsory for all patients on azathioprine, a pharmacogenetic service at a national level was created. There are three underpinning reasons for this:

- Reference Laboratories actively promoted TPMT testing and optimised prices to make it affordable for the NHS.
- Some professional bodies, such as the British Society of Dermatology, have taken the lead in testing, by releasing professional guidelines, recommending clinicians do the testing and, consequently, enhancing user experience and encouraging other clinical professionals to adopt the technology.
- Some NHS Foundation Trusts have decided to establish TPMT pre-screening policies so that any patient entering into treatment with AZA or 6-MP should be pre-screened beforehand.

Nevertheless, although a service already exists, the demand for it would not justify setting up the service at a Trust or hospital level. If we take the example of an average university hospital, with approximately 400 patients taking thiopurines (azathioprine or 6-mercaptopurine) every week, only about four of them are likely to develop an ADR. It is therefore difficult to justify setting up a whole new service in order to avoid the possibility of an adverse event in four or five patients.

Full centralisation of TPMT testing in a single laboratory might not be possible, unless there is a specific policy initiative to do so (respondent 6). In contrast to this, there is a body of opinion that thinks that a TPMT testing service could be run in every hospital, as technology becomes available and cheaper (respondent 10). However, the promoters of specialised services, mainly research laboratories and some groups of clinicians, argue that TPMT services should not be offered in every hospital, because the people who are treated with 6-MP or AZA would be insufficient to create expertise at a local level. However, it would be enough to justify a service that gathers samples from different hospitals across the UK, as this is already set up and functioning (respondent 1).

Iif the demand for testing increased considerably, then there could be an argument for de-centralising TPMT testing into regional laboratories or even into every NHS Trust. On the other hand, TPMT testing could remain restricted to the two reference laboratories, which currently hold the expertise in the UK, provided these laboratories increased their size and resources for testing.

The demand for TPMT testing could increase if:

- NICE granted approval to it and testing was made compulsory in the NHS.
- NICE did not grant approval (either because a technology appraisal concluded that it was not cost-effective or because TPMT testing was not appraised by NICE) but nevertheless, professionals began implementing it and NHS Trusts began reimbursing the cost of the test locally.

However, whether the demand for testing will increase will depend on the results of future clinical utility trials and on cost-efficiency. Whether these results will affect service delivery will depend on political decisions as well as professional lobbying.

In whatever case, at present, the centralisation of TPMT services in these two reference laboratories has advantages:

- Managing a high volume of samples (60 to 70 every day) helps to improve the protocols for the purification of the blood cells, from which the measurements of TPMT are taken.
- The setting up of a routine laboratory for TPMT testing would facilitate the establishment of a routine service where results could be fed back to clinicians within six working days meaning that patients would not have to wait long to get the correct drug and/or dose.
- A large number of samples requires two to three staff fully dedicated to the analysis, which improves the knowledge of how TPMT levels affect drug response, as well as helping to optimise the interpretation of the results, which can be ambiguous when, for example, the laboratory is not informed that a patient has undergone a blood transfusion, or when a patient has already been given the drug and has developed a severe adverse event. In those cases the samples need to be re-analysed and often go for gene testing to confirm the results.

The creation of reference laboratories for TPMT testing did not respond to any initiative of the NHS. TPMT testing services were set up after the Department of Health published a White Paper in 2003 announcing funding for PGx research and encouraging researchers to look for specialised service delivery mechanisms (DoH 2003). At that time, as TPMT testing was one of the first PGx uses known of, the TPMT reference laboratories decided to embark on the test. Therefore, the use of TPMT testing was not a nation-wide decision but the result of certain hospitals or Trusts considering that TPMT testing was worthwhile and therefore starting to screen patients.

> *At present, the NHS thinks locally and not nationally, therefore the centralisation of services, where it does happen in the case of TPMT testing, is not because of a nation-wide decision, but because certain hospitals or Trusts consider it is worthwhile to run a specific test (respondent 24)*

8.4.1.1 TPMT Demand in Secondary Care

At the moment, PGx testing is offered in secondary care (through NHS Foundation Trusts), by different clinical and research laboratories, although TPMT PGx services have been established in an unregulated fashion. The non-existence of specific PGx laboratories (and instead the setting up of PGx testing in other clinical laboratories) is pushing some clinical departments towards specialisation in genetics (respondent 12), although the establishment of PGx laboratories still entails solving various uncertainties, such as what a standard PGx service is and what technicalities it requires.

TPMT testing services in the UK are offered by four main laboratories: the Biochemistry Department at Birmingham City Hospital; the Purines Research Laboratory at Guy's Hospital; the Haematology Department at the Royal Hallamshire Hospital in Sheffield and the National Genetics Reference Laboratory in Manchester. The percentage of TPMT testing per location is the following: London 74.39%, Birmingham 12.6%, Manchester 4.2% and Sheffield 2.1% (Fargher et al., 2007).

The first two are TPMT reference laboratories accredited by the United Kingdom National External Quality Assessment Service (UK NEQAS) and provide TPMT testing services to other hospitals. The cases of Sheffield and Manchester are different. Sheffield is a research laboratory; therefore it is not clinically accredited. It did TPMT testing as part of the ALL2003 trial funded by the Medical Research Council Trial. Therefore, for a period of time they offered the test to patients entered in the trial (MRC, 2007). Manchester is similarly involved in a clinical trial that is assessing the cost-efficiency of measuring TPMT levels in dermatology, rheumatology and gastroenterology, the TARGET Study (NOWGEN, 2005).

Apart from the reference laboratories, which have consolidated demand, the Manchester Laboratory did TPMT testing because it was already specialised in genetic testing and could relatively easily adapt its infrastructure for TPMT genetic testing, although, in contrast to the TPMT reference laboratories, it does not do TPMT testing beyond the protocol of the clinical trial and does not provide TPMT testing as part of a routine service (respondent 14). The Sheffield laboratory, on the other hand, stopped any activity linked to TPMT testing after the trial concluded. One of the respondents argued that TPMT testing is not a national priority for ALL, because the NHS thinks locally. The second reason for this is that there is not enough of a financial incentive for the testing and, once the ALL patients had been

tested as part of the ALL2003 trial, there was no other driver for continuing to offer TPMT testing (respondent 24).

8.4.1.2 TPMT Demand in Tertiary Care

TPMT testing is offered in tertiary care by the North West Regional Genetics Laboratory, who offers technical support and advice to other laboratories within a national network, as well as to the TARGET Study.

8.4.2 Organizational Implications

The implementation of PGx requires important organizational changes associated with the use and interpretation of new forms of testing. However, one of the current problems that genetic testing is facing is that there is no clear definition of what the role of clinicians, pharmacists and laboratories is in relation to the prescription, analysis and further interpretation of a diagnostic test.

For example, at the moment, the haematology and gastroenterology departments of the same hospital may be requesting a genetic test without knowing that the other department is doing the same (respondent 14). The lack of communication leads to information asymmetries and, if a patient, for example, is treated in both clinical units, s/he might be undergoing similar tests in each unit. Implementing communication channels across clinical specialties is important in order to enhance users' experiences and enable better practice.

As the understanding of the linkages between genes and health profiles grows, there is likely to be a growing number of multidisciplinary centres that investigate different aspects of health care genetics. In order to maximise the understanding of the genetics of disease and drug response, it may be necessary to share genetics knowledge among clinical and non-clinical specialists, because grasping the genetics of disease and drug response is complex and requires an understanding of, not only genes, but also gene-gene and gene-environment interactions, and this requires a collaborative effort between experts in genetics and clinicians (respondent 23).

8.4.3 NICE, Conflicting Health Care Systems and Good Medical Practice

As we have seen along the case studies, NICE faces a lot of criticism. This is party the reason why the diffusion of medical innovation is a conflict-ridden process instigated by a clash of opinion between clinicians, patients, policy-makers and regulators, partly because NHS reimbursement policies depend simultaneously on clinical guidelines, peers' opinion and NHS Trust budgets and the three do not always coincide. Under this situation, it is difficult to establish a definition of good clinical practice. This is accentuated when drugs or technologies are not regulated by a NICE clinical guideline. In the absence of guidance from NICE, NHS Trusts have a market mechanism through which they can take decisions on which treatment to reimburse, according to what they think is feasible (for their budget), a mechanism which leads to disparities in technology adoption across the NHS. So, at the same time as there is a well-established reimbursement strategy that recognises NICE as the main body of technological evaluation, which decides on the innovations that should be implemented in the NHS, NHS Trusts operate independently when NICE does not release a specific guideline. There are, however, inconsistencies when it comes to justifying why certain therapies are offered in one NHS Trust and not in another. In that situation, it is difficult to assess what good medical practice means and what good medical standards imply.

TPMT testing is an example of this. NICE has not appraised the technology and therefore, TPMT testing pre-screening is not compulsory, nor reimbursed by the NHS. However, some NHS Trusts have established pre-screening policies and some individual clinicians have started testing.

One of the main drivers for some clinicians who decide to take up TPMT testing, has been personal experience (e.g. a patient suffering from a severe ADR after taking azathioprine) (respondents 4 & 25) or having been involved in any of the clinical trials that included TPMT testing in their protocols (respondents 8 & 25). However, since there is no formal guideline that advocates the use of TPMT testing, but as some clinicians do test for TPMT, it is not very clear whether not testing and experiencing a severe ADR as a consequence of taking AZA, would be considered to be malpractice.

Clinical peer opinion is a strong driver for technology adoption. The lack of consensus about the benefits of TPMT testing across specialties makes the situation more complicated. The

British Society of Dermatology advocates the use of testing in its professional recommendations and, since peer opinion is a strong driver for adoption, it might be possible that not doing a TPMT test in dermatology may be considered poor practice, even though clinical utility has not yet been confirmed in clinical trials (TPMT testing is offered as a "home-brew" test (see section 5.12) and these do not need to undergo clinical trials). In other specialties, such as gastroenterology, where professional bodies do not recommend testing, it might be a different case. So, current differences in opinion about TPMT testing, the fact that TPMT test is a "home-brew" test and, the lack of a NICE evaluation of the test, have made the delivery of TPMT testing services controversial for three reasons:

- The validity of a "home-brew" test does not correspond to the results of clinical trials and therefore the ways in which testing facilities for these laboratory-developed tests are set up, are controversial.
- It is unclear whether a clinician could face a malpractice suit if a patient was seriously ill after taking AZA or 6-MP because s/he had very low TPMT activity and this was not detected before taking the drug.
- It is also uncertain whether a malpractice suit would similarly affect dermatologists, for whom TPMT testing is recommended as gastroenterologists, for whom TPMT testing is not advised.

8.4.4 Changing Practice, Adapting Regulations: TPMT Pre-Screening Policies

The reference laboratories suggest that TPMT testing is cost-effective on the basis that it prevents serious ADRs whose treatment costs are very high. Some clinicians, on the other hand do not agree, claiming that, in particular in the treatment of ALL, ADRs are detected very quickly because patients undergo very regular blood tests, liver function tests and electrolyte analysis. In response to this, the reference laboratories say that, by the time an ADR is detected through routine blood monitoring, the bone marrow may have already suffered a large amount of damage that may be difficult to treat and may, eventually, have fatal consequences for the patient.

As we saw in chapter 5, some studies have shown that TPMT enzyme test is cost-effective, in particular in patients. However, neither of these studies was considered when making the final decision on whether TPMT implementation across the UK. As a result, TPMT testing is

only used locally, through local pre-screening policies, on the basis of the evidence available and the willingness of the NHS Trust to pay for the test. Still, the interpretation of the empirical evidence remains controversial.

Although NICE did not appraise the technology, twenty UK NHS Trusts set up TPMT pre-screening policies for testing AZA/6-MP susceptibility (respondent 1) and already all dermatologists in the UK do test for TPMT. These policies are the result of the consensus about the appropriateness of the test among clinicians, NHS Trust managers, the testing laboratory and the pharmacy of the hospitals, based on scientific data, economic assessments and personal experience (some of the clinicians who decided to use TPMT testing had experienced a patient being seriously affected by an ADR – respondents 4 & 6). The hospitals that have decided to do TPMT testing in all patients undergoing treatment with AZA or 6-MP, reimburse the test locally.

Service provision is as follows: once a TPMT test is requested by a clinician, the patient signs a consent form and a sample is sent to one of the reference laboratories. As was explained in Chapter 4, the laboratory sends a report back within 6 working days, with a narrative interpretation (respondent 1), in which they assign a high or low risk of myelotoxicity and warn of the need for cautious use of AZA or 6-MP, although the report is only a recommendation that the clinician has to evaluate on the basis of other factors, which can be any of these (also see sections 5.1, 5.2 and 5.3):

- The patient is normal (his/her TPMT levels are normal or even higher than normal) and is at low risk of myelotoxicity.
- The patient is at a higher risk of myelotoxicity than normal (TPMT levels are low) and azathioprine should be taken with caution (clinicians often reduce the dose by half).
- The patient is at a high risk of myelotoxicity (levels of TPMT are very low or non-existent) and should not be given azathioprine.

8.4.4.1 Sources of Clinical Demand

As has already been pointed out, the clinical demand for TPMT testing varies across specialties. During the first year of the TPMT service being provided in Birmingham City Hospital, the TPMT referrals came from the following clinical specialties: gastroenterology (66.7%), dermatology (13.6%). rheumatology (12%) and other miscellaneous (7.7%)

(Graham et al., 2004), with increasing demand in the following years. By diseases treated, TPMT testing was undertaken for: Crohn's Disease (27.5%), Ulcerative Colitis (31.9%), Inflammatory Bowel Disease: (4.8%), Systemic Lupus Erythematosus (4.4%), Dermatitis/Eczema (7.2%), Bullous Pemphigoid (6.3%) and miscellaneous (7.6%) (Graham et al., 2004). Further studies also confirm the prevalence of TPMT testing among gastroenterologists, followed by dermatologists and rheumatologists (Fargher et al., 2007).

8.4.5 Challenging Evidence Based Medicine

In the previous section we have seen how we came to the conclusion that diagnostic testing was a critical point for the implementation of PGx in clinical practice. Here, we explore some of the implications that this has on the exiting Evidence-Based-Medicine model of clinical practice.

EBM promises rationality and predictability (McLaughlin, 2001) and offers the possibility to reduce the costs and minimise the risk aof new medical procedures, in particular when these are new and new and there is not enough professional awareness about their use. In section 3.3.5 we described the basis of EBM.

EBM relies in existing evidence as well as clinical experience and how the existing evidence is used for treating individual patients. However, since EBM is not an exact science, it often raises problems of safety and efficacy. For this, although drugs undergo regulatory approval that intends to prove safety and efficacy and, although new drugs go through post-marketing surveillance mechanisms, drugs in the market still face associated problems of safety and efficacy.

The main benefit that PGx offers is that, by means of diagnostic testing, it is possible to predict drug response, as well as it is possible to prevent ADRs. Therefore, if diagnostic testing was widely used in the clinic and if, the adequate drug-test associations were translated into effective tools, PGx could become and effective way of improving clinical practice. Pharmacogenetics could then also be included as an assessment ground as to the suitability of new drugs and medical treatments to individual patients.

8.5 Uncovering the Future of TPMT Testing Services

8.5.1 TPMT Enzyme Tests *vs*. TPMT Genetic Tests

Currently, testing for TPMT enzyme levels (phenotyping) to predict susceptibility to AZA or 6-MP is a much more extended practice than testing for TPMT genetic polymorphisms. In most cases (with the exception of patients that undergo blood transfusions or those whose enzyme levels do not give clear results because other environmental factors may be altering the inherited pattern of TPMT production) phenotyping is more informative. It tells exactly what the levels of TPMT are at the moment of prescribing the drug and these do not always correlate with the genetic profile. For example, a patient who is heterozygous may or may not be a good drug metaboliser and, even if as a precaution the dose is reduced by half in these patients, there is a risk that some patients may remain under-treated because they are heterozygous but have normal levels of TPMT and therefore are good drug metabolisers.

The benefits of phenotyping also include better optimisation of the technology than in the case of genotyping. A reference laboratory can measure enzyme levels in 60 to 70 patients per day and there are procedural standards, as well as improved protocols, for extracting blood samples. The number of samples that undergo a genetic analysis in a reference laboratory is on average, 3 to 5 every week and, even if these laboratories test for the four most common polymorphisms (TPMT *2, *3A, *3B and *3C), there are other polymorphisms that influence drug response that may be affecting how the patient is metabolising the drug. However, due to the lack of a clear standard for clinical utility for genetic testing, these other polymorphisms are not checked for. Analysing all 23 known TPMT polymorphisms would be lengthy and costly. At the moment, the reference laboratories have established a TPMT PGx service at a standard average price of £30.

In terms of demand, TPMT testing is requested most frequently in gastroenterology, followed by dermatology and rheumatology. Among the clinicians who prescribe TPMT testing, a very small minority specifically request a genetic analysis. However, even though phenotyping currently prevails over genotyping, there are a number of studies that are evaluating future options for implementing TPMT genetic testing services. Firstly, the TARGET Study) is assessing the cost-effectiveness of phenotyping vs. genotyping.

Secondly, some cost-effectiveness studies have shown favourable results towards the implementation of TPMT genetic analysis, in particular that which tests the four most common polymorphisms in patients with Acute Lymphoblastic Leukaemia (ALL).

Therefore, in the future, the evolution of knowledge on TPMT mutations and drug response, the increase in technology throughput, and the availability of data from clinical trials and cost-benefit studies, may make it possible to exploit TPMT genotyping further in clinical practice, if the benefits of genotyping outweighed those of phenotyping. However, with current knowledge and technical expertise, the way in which it may happen remains uncertain.

8.5.2 Tackling the Knowledge Gap

Even though the TPMT gene contains 23 known polymorphisms, with the evolution of technology it might be possible to test for more than four mutations as routine clinical practice. The current release of an IBD® Chip (that includes some TPMT genetic polymorphisms), which assesses susceptibility to inflammatory bowel disease (IBD), could be a possible example of future options for TPMT testing delivery. If more TPMT genetic mutations were known and were integrated efficiently into a biochip that could give relevant information about drug response, then there could be an argument for shifting current ways of phenotypic testing into more genetic-oriented approaches. However, in order for this to happen, the benefits of the genetic analysis would need to outweigh the existing phenotypic analysis, because if it did not, and phenotyping still proved more efficient, the substitution of one technology for another would not occur.

8.5.3 TPMT "Home-Brew" Tests vs. TPMT In-Vitro-Diagnostics

In the UK, TPMT testing is provided as a laboratory developed or "home-brew" test. However, in the US, a company called *Prometheus* offers commercial TPMT phenotyping and genotyping kits (it holds a US patent). However, in the UK the market for TPMT testing is restricted to "home-brew" tests, and there is no private patent holder. There are several reasons for this:

- Firstly, the DoH, as a result of a White Paper released in 2001, announced funding for PGx projects with a clinical application. TPMT testing was at the time among the candidates because TPMT was one of the first biomarkers identified as

intervening in drug response. The interest of the research community was attracted and some years after the White Paper was released, the community started offering TPMT testing and running a PGx clinical trial. In 2003, the TPMT reference laboratories started offering TPMT testing services, catering for the necessity, anticipated by the DoH, of translating PGx into clinical practice. Later, in 2005, the North West Genetics Knowledge Park (NOWGEN) launched the TARGET Study.

- Secondly, TPMT testing is offered by public NHS laboratories because there is no competition from the private sector to offer a similar test. TPMT testing assesses the response to AZA and 6-MP, both relatively cheap and off-patent drugs. The lack of interest from the pharmaceutical industry in co-developing a "new" AZA or 6-MP, together with a test for TPMT, was an incentive for the NHS reference laboratories, who did not foresee competition from the private sector.

In the future, if new knowledge about the genetics of drug response becomes available, private companies might become interested in investing in TPMT testing, in particular if TPMT mutations were discovered to be involved in the response to new drugs. If this was the case, and a private company patented a genetic sequence of TPMT, this could affect public service provision and therefore, the TPMT services currently offered by the TPMT testing laboratories.

If a company held a patent of a TPMT genetic sequence but the reference laboratories still offered TPMT phenotypic analysis, the question would then be who would request a phenotypic analysis and who would request a genetic analysis. Much would depend on how informative the genetic analysis was in relation to the phenotypic analysis, its relative costs, how much clinical demand was and which of them the NHS would be willing to reimburse.

8.5.4 A shift in Service Provision: De-Centralisation of TPMT Testing

Why not centralise TPMT testing? Despite the intention of the White Paper to promote PGx, the NHS is dominated by a market mechanism driven by utility, which favours tests that target a broad range of the population and of diseases. Therefore, the objectives of the White Paper to translate genetics research and personalised medicine into the clinic were not accomplished in all cases, because the NHS works on priorities and, on these grounds, it would rather promote a test that has an impact on a large number of patients.

The convenience of setting up a centralised PGx service, like the Sanger Centre, has already come under discussion, although this might not be feasible because, often, expertise derives from local research, which is difficult to centralise. At the same time, clinicians are often interested in problems shared by certain local populations causing them to decide to start testing locally and eventually set up certain services at a local level. Clinicians are very interested in the conditions and genetic diseases they see in their local population because that population may have a particular disease that is prevalent and important to their community. If they are all linked to the same centre, that centre develops an expertise in seeing these patients and also gathers biological material which allows them to do research, and may allow them to develop a new service. Some of the expertise owned by the National Genetics Reference Laboratories, for example for cystic fibrosis, is very difficult to centralise because there are centres already testing for cystic fibrosis. When the genetic origins of diseases or conditions are not well determined, there is no specific action or expertise which can enable the interpretation of the genetic information to a broader context (respondent 14).

As more genetic tests become available, it may be necessary for every hospital to offer a genetic testing service that gives coverage to all clinical specialties, but at the moment technology is still expensive and there are gaps in the knowledge. The way these services are growing depends on who has got the financial resources, whether they are doing research into PGx service delivery, and whether the consultant in charge foresees a benefit in doing the test and acts as a lead user. For this reason, it might be worth thinking about setting up large genetic laboratories from the very beginning and directing money to those laboratories to set up specific services (respondent 10). However, centralising a service once it has been set up might be more difficult than if it is created centrally from the very beginning. Some of the previous experiences in cystic fibrosis show that, even if there is a national demand for a test, once scattered services are set up it is difficult to close them just because they do not have enough work to justify their continuation. In addition, hospitals like to have a specialist facility that gives them prestige and brings in money (Hopkins, 2004).

One solution for overcoming the problems associated with an eventual radical centralisation of services would be to share testing facilities between four or five laboratories so that each of them could make a small profit and this could avoid losing a small laboratory in favour of a bigger testing one (respondent 6). This could also eventually

be done by setting up super-regional laboratories, instead of having the service completely centralised in one place (respondent 10).

> *…there is a lot of expertise that goes into doing these tests and you will need to move a lot of that expertise which is attached to a lot of clinics…that's why you wouldn't put it all in one place at the moment because it has not reached the state in which the technology and the genes are well enough understood to be able to be "black boxed", to be able to say, "these are all the variables, this is everything we need to know, I give it to a technician and they can do it". This might be the case of some conditions which are better understood but I don't think it is the state of play with all the other rare diseases and some of these are the ones that are coming, like TPMT testing, and that's why you wouldn't centralise it… (respondent 6).*

8.5.4.1 Genetic Testing at the GP

General Practitioners could apply pharmacogenetics and do genetic testing in order to improve drug prescription, adjust doses and prescribe the right dose from the beginning. However, at present this is unlikely to happen because:

- It is necessary to have more knowledge on how genetic profiles affect drug metabolism (respondent 10). Before starting PGx at a primary care level, it is necessary to be able to put the genetic risk factors together with the environmental ones, to give some sort of meaningful answer, and to be able to put those factors together in a sort of algorithm that someone could act on, although that would be very difficult (respondent 6).
- GPs are often overloaded with patients and they might not provide the same quality of service as specialised genetic clinics. In breast cancer, for example, nurses are very well trained to take a family history and they know how to refer on, but a GP might not have the time to take the family history into account in the same way that is provided currently by specialised nurses in the Regional Genetic Services (respondent 23).
- GPs have, broadly, little expertise in genetic testing (Hedgecoe, 2006), except for some who are interested and have a specialisation in it. There may be some interest in certain disciplines, but not in a broad enough sense, and there would need to be more education (respondent 6).

In the future there is a possibility of PGx being developed in primary care, but only when no more than two genes are being analysed. Finding mutations in more than two genes would require more advanced technology and it is likely that undertaking this kind of analysis in a GP practice would not be possible. In any case, the use of PGx in primary care (probably through points-of-care) would require clear guidelines for interpreting the results of the test as well as prescribing on the basis of those results. If there are more genes involved in the interpretation, this is more complicated and there would be no way of analysing them as points-of-care in a primary clinic (respondent 13).

> *…there is a huge dream for PGx, which is that "you come to me, you've got a disease, I do a gene test, I say to you "don't use that drug" and you get the gene that predicts the drug you will use very well". I think that it's the way forward…clearly is the way forward but … we are a long way from getting it into the clinic (respondent 22).*

8.5.4.2 Genetic Testing at the Pharmacy

Genetic testing at a pharmacy seems feasible in the case of single gene PGx, through SNP analysis, where single mutations could be analysed in portable kits (points-of-care) (respondents 10 & 13). However, this would not be possible when testing involved more than one gene. At the moment pharmacies can take blood pressure measurements and sell cholesterol testing kits over the counter and, as technology advances, SNP analysis could also be offered at the pharmacy. These tests would measure whether there were mutations in a very specific region of a gene (multiple gene analysis would probably not be feasible at the pharmacy). This would require strict quality control measures. The decision to do SNP testing at a pharmacy would have to come, under the present system, from the general practitioner or whoever prescribed it. However, if we moved to a situation where pharmacists did a lot of prescribing, the doctor could do the diagnosis and transfer the prescribing to the pharmacist afterwards, so testing could then be done in community pharmacies instead of at the GP clinic.

8.5.4.3 Private Service Provision

In the UK patients are referred to private companies when particular forms of genetic testing cannot be performed within the NHS. This is the case for breast cancer screening services, when patients with a family history of breast cancer have less than a 20%

probability of inheriting a breast cancer mutation on the genes BRCA 1&2. In these cases, the NHS does not provide coverage because, according to NICE, these family members are not at a high risk of breast cancer and their guidelines do not recommend testing (respondent 23). In these cases, women often want to go for testing and pay for a test to be done by Myriad Genetics, the company which commercialised the BRCA 1&2 tests.

Another example of genetic testing by private companies having potential is leukaemia sensitivity assays. Few hospitals in the UK do leukaemia sensitivity assays because not every hospital has the necessary equipment and expertise to do it. Every child diagnosed with leukaemia goes through a test to look for sensitivity to a panel of drugs. One of the sensitivity tests used to be done in a hospital but when the hospital was rebuilt and the laboratory demolished, no new facilities were constructed, which ended the provision of the sensitivity assay for leukaemia (respondent 24).

In order to overcome the weaknesses in the system, some clinicians advocate that genetics testing be done by private companies, which would allow for standardisation of procedures, and ensure a very high quality and reliable testing (respondent 24). The defenders of the public health service, on the other hand, maintain that if a test were to be done by private companies they would have to do it for many more patients in order to justify the costs of testing (respondent 1). In opposition to this, some of the interviewees claimed that it is likely that the costs of genetic testing may be cheaper if done by private companies, which would not necessarily provide services exclusively to the NHS in the UK, but also to other countries. In this case, private companies may be able to offer tests more cheaply than public laboratories (respondent 14). Strong competition for genetic services might mean that if the NHS or any other health care system did not adapt to the new genetic technologies, it might then be more feasible to outsource these services to the private sector, where there would be competition and this would be an incentive to improve the quality of the service.

Nevertheless, in the UK, genetic testing by private companies remains controversial and generally is confined to private health care providers, which account for a minority of UK health services. Where possible, "home-brew" testing prevails over commercial diagnostics, mainly because of the costs, but also because of ethical issues.

Companies providing genetic services assert that they do not store any information and that, when the results of a test are sent back to the patient, samples are kept for some time

for quality control purposes and then destroyed (respondent 20). However, there is still a lack of regulation to protect the patient. For example, in the case of breast cancer screening, Myriad Genetics does not ask patients whether they want their samples to be kept and, even if the DNA samples were kept by the company, there is no directive that would protect the patient and prevent companies from storing these samples (respondent 23). For this reason, the possibility of the NHS outsourcing genetic testing services to private companies, still poses major ethical concerns.

The supporters of private service delivery do not see major problems in this respect, if the information is well encrypted from the very beginning, as is currently done in public clinical and research laboratories (respondent 24). Although, even in this situation, there is always an issue over who owns that information and who will have future control over it, especially in cases where informed consent does not cover the possibility of future use of the DNA sample. Nevertheless, on the ethical side, there are some lessons to be learnt from established NHS genetic services in the UK, such as the breast cancer genetic screening services, where all information is treated under strict controls of confidentiality and where access to any medical record or a family's genetic history requires the consent of the patient. Even after this consent has been obtained, the information remains within the hospital and cannot be shared with other hospitals (respondent 23).

8.5.4.4 Biochips for TPMT Testing

Biochips might be an option in future PGx applications, although in the case of TPMT, a biochip to do TPMT testing on its own does not seem to be the best option. Firstly, because the use of TPMT phenotypic tests prevail over genetic tests and, secondly, because, although it being technologically possible, developing a chip with only the four most common TPMT mutations that the reference laboratories are looking at, would not be economically feasible, because biochips can hold hundreds of mutations.

There is a DNA chip that permits the prediction of the evolution and prognosis of inflammatory bowel disease (IBD) as well as the selection of the most appropriate treatment for each individual. This device, the IBD® Chip, the first diagnostic DNA chip developed worldwide, was launched in 2006 by the Spanish company Progenika Biopharma, in collaboration with the Hospital Clinic de Barcelona. It analyses 61 polymorphisms related to IBD, some of which are TPMT polymorphisms.

Although the demand for biochips is still low, the interest in them is increasing. After the IBD® Chip was commercialised tThrough the EU's Sixth Framework Programme, a €2.5 million project was approved aimed at validating the IBD® Chip within the European Community. The project, which ends in December 2009, is led by the Hospital Clinic and IDIBAPS (a research centre formed by the Generalitat de Catalunya, the Ministry of Health and Innovation, the University of Barcelona, the Institute of Bioscience Research (IIBB-CSIC) and the regional innovation department DIUiE) (IDIBAPS, 2006).

The approval of a European project that aims to assess the clinical validity of the chip in a European context, highlights the fact that, although the approval of diagnostic tests occurs at a national level, the clinical utility of the test is assessed at a European level, which is an indication that regulations on diagnostic tests might need to be harmonised in the future. Running European projects and clinical trials is the first step to achieving such a target.

8.5.4.5 Genetic Counselling: Enhancing NHS Capabilities

One of the shortcomings of private service provision is that companies cannot offer genetic counselling, which is an expertise that resides in the NHS. If these companies offered testing, they would save the associated costs of counselling and testing would be more cost-effective for them. So, if it became mandatory in the NHS to provide genetic testing together with a counselling service, then companies would do the testing and somebody else would have to interpret the results (respondent 14). At this stage, the NHS could "monopolise"[21] the service and prevent companies from creating private monopolies by protecting the use of "home-brew" tests done in hospitals (because any genetic patent holder can prevent any company or public laboratory from using the specific genetic sequence over which they hold the patent). Therefore, the NHS could say that genetic testing has to be accompanied by counselling. If that happened, private companies would not be able to have exclusivity over a genetic service and would need to rely on public laboratories (Martin et al., 2006).

[21] The term "monopolise" here refers to the establishment of certain conditions for testing, under which private provision could be contemplated, but always under the control of the NHS.

8.6 Institutional Frameworks: Country Comparison

The purpose of this last section is discussing the differences in TPMT adoption across the UK and Spain, in the context of their particular institutional context. While the scientific and technological developments of PGx occur at a global level, their translation to the clinic is heavily regulated by institutions at a national level. This explains the different approaches to TPMT testing in both countries.

8.6.1 UK and Spain, a different TPMT strategy

According to the levels of TPMT in the blood, patients are classified into three categories: those who have very low levels or no TPMT in the blood; those who have lower levels than normal and, those who have normal levels (or even higher than normal). According to this phenotypic classification, the recommendation is the following:

- Patients with no or very low TPMT (0.3% of the population) should not receive AZA or 6-MP because of a high risk of suffering a severe ADR. If a patient that fits this profile is already taking the drug, s/he should receive an alternative treatment.
- Patients with lower levels of TPMT than normal (10% of the population) should receive reduced concentrations of the drug in order to minimise the risk of ADRs.

This was the guidance followed in the UK. In Spain, however, the situation was different. UCB Pharma became interested in TPMT testing as part of a strategy to "relaunch" AZA and "renew" its drug portfolio. The company was seeking to find new drug indications and launched a clinical trial, in which, they investigated the possibility of, not only identifying the non-metabolisers of the drug, but also finding good responders who could benefit from an increase in doses. However, this increase in doses is contested. Although some clinicians involved in the clinical trial subscribe to it, which indicates some of the feedback mechanisms that occur between the drug industry and clinicians during the process of drug development, TPMT testing is not a widespread practice in the clinic. Although some researchers and some laboratories have suggested that patients may benefit from increased doses, no confirmatory data is available and the matter is still contested. However, the fact that this increase in doses may occur in Spain and not in the UK is due to a lack of a regulatory system comparable with NICE in the UK.

In the future, if it was ever confirmed and validated that patients with higher levels of TPMT could tolerate a increase in drug doses, then the pharmaceutical industry could become interested in co-developing TPMT tests together for with off-patent drugs such as AZA. If that were to be the case, the drug industry may have a business case to start investing in PGx for generic drugs, which at the moment has not attracted as much interest as PGx for new drugs.

8.6.2 Institutional Setting, Country Differences

There are important differences between the UK's and the Spanish health and pharmaceutical systems that influence the translation of PGx:

- The centralisation of the UK system and the de-centralisation of the Spanish system, which leads to regional differences in service provision.
- The role of NICE in the UK and the role of the AETS in Spain. NICE is involved in reimbursement policies and bases its decisions on cost-efficiency. In Spain, the AETS has a more consultative role than NICE and responds to specific requests from the Ministry of Health. Although not compulsory, cost-benefit studies are required for reimbursement decisions.

In terms of PGx promotion, in the UK, the release of the White Paper in 2003 encouraged public laboratories to enhance PGx understanding and service delivery. In Spain, there was no similar initiative. As a consequence, and due to the differences between the Spanish and the UK's health care and pharmaceutical systems, the patterns of TPMT testing are different in the two countries:

- In the UK, public TPMT reference laboratories were set up, taking advantage of the interest from the DoH in PGx services. In Spain, there was no similar initiative to give public laboratories an incentive to invest in PGx and, instead, a private company, UCB Pharma, was the initiator of TPMT testing.
- While the driver for the reference laboratories was to offer an affordable PGx service, the drivers for UCB Pharma were renewing its drug portfolio and labelling an off-patent drug (AZA) with a PGx component (TPMT testing).
- TPMT testing was not evaluated by either NICE or the AETS. However, implementation was higher in the UK. The UK reference laboratories tried to reach

as many clinical specialties as possible, whereas in Spain, UCB Pharma targeted gastroenterologists who were willing to take part in the AZA/TPMT testing trial. From the information gathered, it seemed that there was not a large amount of knowledge about TPMT testing among the clinical community if they were not involved in the clinical trial.

- The demand for testing was also much lower in Spain than in the UK. After the AZA/TPMT clinical trial ended, a private laboratory, Cerba International, began to offer TPMT testing (only enzymatic analysis). The demand came almost exclusively from gastroenterology, while in the UK there was demand from gastroenterology, dermatology and rheumatology.

As final remarks, we could conclude the following:

- From the supply point of view, the differences in service provision among countries indicate that public intervention (e.g. the UK White Paper) is an important factor in shaping PGx delivery in public health care systems. When such public mechanisms are not so strong (as in the Spanish case in comparison with the UK case), other private interests emerge and influence the delivery of these services.
- While the motivation for the UK TPMT reference laboratories was to set up a PGx service available to any clinician prescribing azathioprine (and also 6-mercaptopurine), for UCB Pharma, supporting TPMT testing was a way of obtaining a better position in the drug market and improving azathioprine's sales. So, while the UK TPMT reference laboratories pursued a long-term strategy, through which they aimed to increase the understanding of TPMT testing among the clinical community and the demand for testing, UCB Pharma pursued a short-term strategy (a change in the technical specifications of the drug that included information on how levels of TPMT might affect drug response), where any further diffusion of the knowledge of the benefits of TPMT testing was not contemplated.
- From the demand side, public intervention does not seem to affect the acceptance of PGx among the clinical community. In the UK, the degree of adoption of TPMT testing varies considerably among dermatologists, rheumatologists and gastroenterologists, although TPMT testing is equally available to all clinical specialties. The acceptance of TPMT testing among the clinical community depends on factors such as the severity of the disease/s for which azathioprine (and

therefore TPMT testing) is targeted, the existence of other competing drugs and peer opinion, as published in professional guidelines.

8.7 Summary

In summary, we can say that the implications of PGx are multi-dimensional since they affect innovation processes from the stage of product development to the point of service delivery. The discovery of biomarkers of drug response is producing incremental changes that are contributing to the development of more targeted drugs (or "Minibusters") with a reduced number of side-effects. Nevertheless, in order to maximise the benefits of a radical innovation such as PGx, more scientific efforts and technological developments are required, so that its potential can be translated into drug development processes.

PGx, personalised medicine and the co-development of drugs and tests also requires incremental changes in the existing drug and test regulations as well as in current post-marketing surveillance and pharmacovigilance mechanisms. Regulatory agencies, such as the EMEA in Europe or the MHRA in the UK, would need to adapt to the requirements of new technologies by developing new regulations, harmonising regulations across Europe, and encouraging better practice contributing to a better use of PGx (e.g. the submission of PGx data by the pharmaceutical industry during the drug approval process and more systematic reporting of ADRs through systems such as the Yellow Card Scheme in the UK).

Clinical practice will also be affected by the implementation of PGx. Diagnostic testing will require new testing facilities, new skills and in general, a stronger understanding of the genetic and or phenotypic factors associated with drug response. Clinicians will need to develop closer communication channels with the laboratories that undertake PGx testing as well as with the pharmacists who prescribe the drugs or adjust the doses, possibly by enhancing information systems such as electronic medical records. Clinicians will also need to enhance communication and networking across specialties, in order to disseminate the benefits of PGx through user experience. They will also need to enhance linkages with the governance system and agencies such as NICE, to agree standards of testing and define the criteria of good medical practice.

Finally, PGx can offer an array of possibilities for service delivery, from the de-centralisation of testing facilities to a few NHS hospital laboratories, to the de-centralisation of services to the GP, the pharmacy or the industry. This is, however, not free from controversy.

All the incremental changes that are in process and will need to occur before PGx is implemented in service delivery are necessarily underpinned by the scientific and technological advances that are driving product innovation, as well as by the social, economic, ethical and regulatory aspects behind the operational and organisational processes that will lead to new mechanisms of service delivery.

Chapter 9. Outcomes of an investigation into the diffusion of PGx into the clinic and some policy ideas for the future

As we introduced in chapter 1, this research intended to adopt an approach that consisted on analysing the barriers that we believed hampered the translation of PGx from drug development into service delivery. By using the STEEPV acronym, we intended to group these barriers according to the scientific, technological, economic, regulatory, political and ethical factors that influence PGx development and delivery and to give answers to the hypothesis presented in section 1.2. This chapter will then give answer to the three main research questions, as well as provide insights about future uses of PGx in clinical practice, under a diffusion of innovations perspective.

9.1 Tackling the Research Questions

The progression of Pharmacogenetics from its current relatively undeveloped and insecure place in the delivery of health care into widespread use is a hazardous journey as this research has illustrated. The research set out to identify the hazards that PGx faces, through elucidating, with the use of two case studies, the three specific questions raised in Chapter 1. For convenience these are repeated here as follows:

1. What are the main enablers and barriers that facilitate and/or hamper the use of PGx in the case of azathioprine/TPMT and Iressa® and Tarceva®/EGFR in clinical practice?

2. How are these controversies articulated by the different actors involved in drug development and service delivery and how is this articulation shaping the process of technology diffusion in the case of TPMT and EGFR testing?

3. How may the controversies around TPMT and EGFR testing may be generalised to a higher level of policy analysis, to inform policy decisions on how PGx service delivery might be implemented in a public health care system such as the NHS?

These three questions are inter-related. The purpose of this chapter is to draw together the inter-relationships that have been identified through the case studies of AZA/6-MP/TPMT and Iressa®/Tarceva®/EGFR. For clarity, AZA/6-MP/TPMT relates to conditions of the autoimmune system and Iressa®/Tarceva®/EGFR to NSCLC. These case studies have enabled the identification of the current controversies and future uncertainties (together with their influences) that surround PGx, and explanations of why TPMT and EGFR testing are critical points in the socio-technical system of PGx. Figure 9.1 illustrates this.

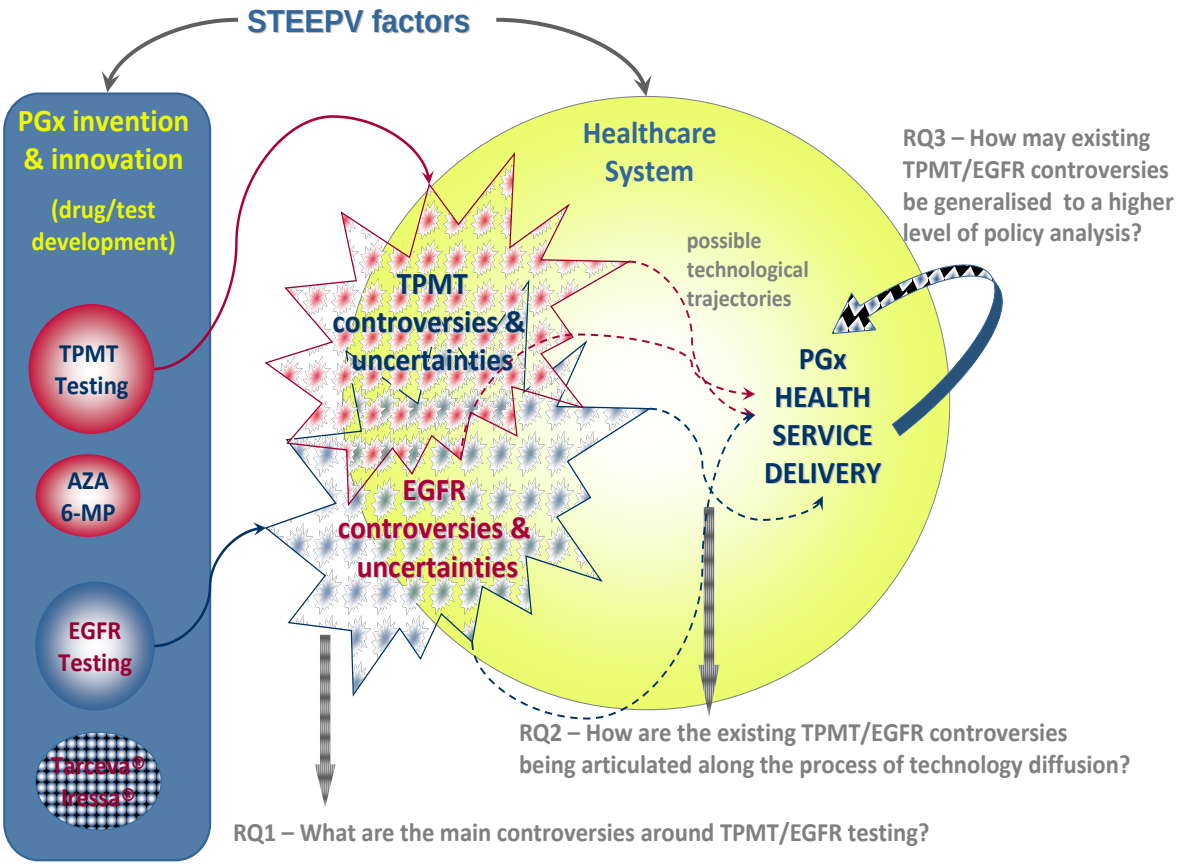

Figure 9.1: Illustration of the research questions in the context of PGx innovation and health service delivery. STEEPV factors stand for: Social, Technological, Economic, Ecologic, Political and Values.

As figure 9.1 indicates, in first place, we have identified the existing controversies and uncertainties that underlie the current use of TPMT and EGFR testing, and to later on, try to analyse possible technological trajectories that may lead to more systematic forms of PGx service delivery through a public health system. However, the definition of these

technological trajectories face a number of unresolved barriers (defined by the elements that underlie the STEEPV acronym), which have been at the core of the discussion in chapter 8. Finally, through the definition of policy recommendations, we have intended to link the existing patterns of innovation, uncertainties and controversies with a macro-level of policy analysis where we could extract some common ground among both cases studies.

This chapter synthesises ideas about how PGx and PGx testing may be diffused more widely into the clinic with consequences for health care delivery, although there is no attempt to place this in any time horizon. The question of diffusion and its associated problems has been answered in an integrated, rather than individual way in chapter 8. Taking into account the factors that underpin the STEEPV acronym, we aimed to highlight the critical points at which PGx becomes controversial (both at the point of drug development and service delivery). Chapter 8 also aimed to provide some hints on how future TPMT and EGFR testing services may uncover, to finish by identifying country differences among the UK and Spain, which will influence these. All of this responds to the first two research questions.

The chapter presented here focuses on more general aspects of PGx, as addressed in the third research question. To create this synthesis, it has been necessary to extract common ground across PGx and PGx testing, which, will serve to inform suggestions for policy making relating to how PGx treatments could be delivered to patients through a public health care system such as the NHS.

9.2 Pharmacogenetics, a Radical Innovation

This section is dedicated to explaining why we considered PGx as a radical innovation and why it is disruptive with the existing drug development and service delivery mechanisms.

As we have seen in chapter one (see Figure 1.1), PGx has been defined as following two technological trajectories. They both coexist, although PGx for enhancing drug efficacy (or the use of PGx to improve the efficacy of drugs under development) is expected to be considerably more common (Lindpaintner, 2003) than PGx to improve the efficacy of licensed drugs, since the incentive for companies to invest in diagnostic testing that can potentially reduce their market is not so high.

Even though there are some exceptions, such as the HIV drug abacavir - Ziagen®, a drug for which a PGx application was found after it was marketed, the pharmaceutical industry is largely concentrating its PGx resources on drugs being developed now, rather than on drugs which are already off-patent or exposed to competition from generics. The fact that there is not much PGx information on generic drugs at the moment (although this is growing) (Human Genetics Commission, 2002) is an indication of this current move by PGx towards new drugs.

Public research in PGx seeks institutional support that encourages clinical studies in the area of generic drugs (drugs which are currently off-patent and open to generic competition), although at the moment there are two important weaknesses that hamper this (Hopkins et al., 2006):

- There is a lack of incentives to introduce academic research results on genetic determinants applicable to existing drugs.
- It is unknown how the genetic determinants applicable to existing drugs could be incorporated into regulatory decision making to improve the use of drugs that have a PGx component.

In order to overcome these weaknesses, in the UK, the DoH has formed an expert Advisory Group on Genetics Research (AGGR) that advises both the DoH and the NHS.

These two trajectories define the current pathways that PGx developments are following, although PGx is still at an early stage and few applications have reached the clinic. So, in the future, with the emergence of new drugs, new tests and drug-test associations, other technological options might emerge, because PGx and personalised medicine are driven by the availability of diagnostic tests and these can take several forms:

- Testing for drug metabolism (e.g. cytochrome P450 testing), which at the moment occurs mainly during pre-clinical studies. P450 are a group of proteins involved in the metabolism of a great number of drugs in the liver. Mutations in the genes that code for the proteins of P450 lead to differences in the response to these drugs.
- Testing for anti-viral drug resistance, as in the case of abacavir - Ziagen®, used to treat HIV patients.

- Cancer testing to guide the development of "new generation" cancer drugs: Herceptin® (trastuzumab) for breast cancer, Glivec® (imatinib) for chronic myeloid leukaemia or Iressa® and Tarceva® for non-small cell lung cancer.
- Testing the response to therapies for other diseases: azathioprine (AZA) therapy for autoimmune diseases and acute lymphoblastic leukaemia (ALL), albuterol therapy for asthma, clozapine for schizophrenia or statins for hypertension.

The wide variety of testing options and consequently, PGx applications, has served to say that, even though there are two technological trajectories to which PGx adheres, PGx applies on a single case basis (Hedgecoe, 2004) because the nature of the disease, the drugs and the tests in each of the cases is different.

9.2.1 The Emergence of PGx

PGx emerged as a technology that followed either of two technological trajectories (Hedgecoe and Martin, 2003): improvements in the understanding of disease and drug response through better approaches to drug target discovery and drug development (Shah, 2004) or new drug-test associations to improve the safety and efficacy of both licensed drugs and drugs under development (Lewis, 2003, Webster et al., 2004). PGx and personalised medicine promised to offer safer and more effective drugs, more streamlined drug development processes and, eventually, also rescue drugs that have been removed from the market for safety reasons (Buchanan et al., 2002), with the expectation that the overall costs of drug treatment should also decrease, on the assumption that the increased efficacy of personalised medicines will offset the higher prices of drugs: by reducing the costs of hospitalisations associated with associated with ADRs (Bukaveckas, 2007). In the UK, the Department of Health (DoH) also strengthened the importance of genetics and personalised medicine.

> *"As our understanding grows about how genes and drugs interact, patients could undergo a genetic test to predict their response and help ensure that the medicine and dose is right first time. This should improve outcomes, reduce wastage and help avoid serious side effects. New pharmaceutical products linked to a genetic test are likely to become available within the next five years. Advances in genetics will lead to new drugs and novel therapies. It will allow the development of gene based drugs and treatments targeted at the disease-causing fault rather than at the control of symptoms" (DoH, 2003).*

However, in reality, few PGx treatments have reached the clinic (Allison, 2008). There are

important differences between what some anticipated would happen, and what it is really happening in clinical practice. There is a big gap between what the opinion leaders and the promoters of PGx thought was possible, what the patients and the lay public thought might be desirable and what those within health care systems believed was feasible.

If we acknowledge that, the development and uptake of medical technologies is a complex system, which involves scientific research and technological development, new business models and market mechanisms, regulations and changes in clinical practice, then, the question to follow would be: Why did some opinion leaders anticipated huge benefits from PGx, without knowing whether, the opportunities that were arising from research would be able to meet the needs for new and more effective therapies and without having a fully-fledged understanding of the implications of PGx for service delivery?. The question to follow would be: why some other groups were more sceptical about the benefits of PGx?

The first question could be understood under the explanation that expectations accentuate when new technologies imply radical innovations, such as PGx. The second question refers to the the fact that, different groups of individuals hold a different degree of expectations and here the conflict. Some people anticipate huge benefits from PGx, while others remain sceptic.

Radical innovations hold a high degree of uncertainty and, although they are formed by a series of incremental innovations, they imply a break from current market structures and this requires collective agreement (Jolivet et al., 2003) and social learning processes (Rip, 1986) that are difficult to anticipate. For this, expectations are often used to mobilise resources, attract interest and legitimise visions that illustrate desirable outcomes for a particular technology. When a new technological opportunity emerges, there is strong uncertainty about its use, about its risks and benefits and there are no stable networks to support it. For this reason, the protagonists of a technological opportunity need to formulate promises and create hypothetical situations in which the technology might be developed, giving a particular use for it, anticipating its users and the whole socio-economic context in which this may happen. It is then that a new technology's sponsors create "protected" spaces (Geels and Raven, 2006) where further R&D activities may take place. Such protected spaces will then form "niches" for radical novelties (e.g. new market niches) and, when the development in these niches results in robust technologies, they can enter mainstream markets. If promises are accepted, they are translated into goals,

specifications, requirements and a shared agenda for an emerging field: this has been defined as a "promise–requirement cycle" (van Lente, 1993).

However, the implementation of PGx in the clinic will require that all the social agents involved in drug development and service delivery, develop, and implement, the necessary capabilities that will enable the use of PGx in practice. However, because these social agents (researchers, companies, clinicians, regulators, policy-makers and patients) have different levels of involvement in the technology and different levels of knowledge and expertise, social learning is aimed at exchanging information and knowledge to align positions for the benefit of service delivery.

9.2.2 Incremental Changes towards a Radical Innovation

Whatever the technological trajectory, PGx implies a substantial change in the way drugs are prescribed. The current model of drug prescription relies on assessments of symptoms on the basis of medical assessments and clinical tests. However, this approach is not always optimal because, although the fact that current drugs (also defined as "blockbusters" because they aim to target a broad number of patients, as opposed to "minibusters" that aim to target smaller sub-populations) are designed and proven (through clinical trials) to be effective in the treatment of particular clinical conditions, sometimes they fail in their purpose and cause adverse events. When this happens, alternative drugs need to be searched for, although the success of achieving a good response to these alternative drugs cannot be pre-determined either. The individual response to mass-market "blockbuster" drugs cannot, then, be predicted a priori in all cases. Even though clinical trials aim to provide statistical evidence on the safety and efficacy of drugs (one of the principles of Evidence Based Medicine relies on the results of clinical trials), the evidence is limited to a sample population and different drug responses may not always be picked up during clinical trials. For this reason, the model of prescription of "blockbuster" drugs has been defined as a "trial and error" approach.

PGx, then, proposes an improvement in the rate of drug response by pre-screening patients and selecting those with the potential to respond well before any drug is prescribed. If it is possible to determine who is likely to experience an ADR, then this could be avoided ex-ante, instead of having to find alternative treatments once the patient is undergoing an adverse event, and while dealing with the adverse event itself. Alternatively, if it is possible to determine who is likely to have an optimal response to a certain drug and who is not,

drugs could be targeted only to those who respond well (these drugs are defined as "minibusters"), avoiding a lack of drug response and patients being under-treated. These, then, are the consequences of the two aforementioned technological trajectories: PGx to improve the safety of drugs (or the avoidance of ADRs) and PGx to improve the efficacy of drugs (or the targeting of treatments only to those who respond well).

But, in order to follow either of the two technological trajectories and achieve their outcomes, some tools (among other elements, which will be discussed more extensively later in the thesis) are necessary. PGx and personalised medicine would first require an understanding of the genetic and/or phenotypic origins of drug response, so that new relations between genes, phenotypes and drugs can be established. Subsequently, PGx and personalised medicine will need the transfer of the knowledge about these drug-gene/phenotype relations into technical instruments (or diagnostic tests) that can effectively assess how a patient is likely to respond to a drug. Diagnostic testing then becomes a crucial element in targeting the right drug to the right group of patients who not only share clinical symptoms but also have a common genetic and or/phenotypic profile that affects their response to drugs.

One of the questions this thesis aims to answer is, why PGx has not been fully translated into the clinic if it can potentially benefit, both the pharmaceutical industry which, although being highly profitable (Smith et al., 2009), is suffering from a decrease in the number of chemical entities to the market (Di Masi et al., 2003a), and also the health care system (Roses, 2000, Lindpaintner, 2003), for which treating adverse drug reactions (ADRs) represents an important economic burden (Pirmohamed et al., 2004).

In this chapter we are hypothesising that, PGx is a radical innovation because it implies a considerable change in the way drug development and service delivery occurs. The process of drug development takes between ten and fifteen years and, before a new drug is approved, a series of incremental inventions, in which many players have a role, occur. No radical innovation can exist without a collective effort that contributes to the radical outcome (e.g. a new drug, a new PGx treatment). So, in order to achieve the major changes that PGx requires, it is necessary firstly to target the incremental changes (e.g. the discovery of new molecular biomarkers associated with a drug response) that contribute to the final "radical" outcome (e.g. the inclusion of those biomarkers into drug development and the marketing of a new PGx drug).

PGx needs diagnostic devices that determine who is at risk of an ADR and who may potentially respond well to a drug, but even with the necessary technical knowledge, the translation of PGx into clinical practice is likely to be a lengthy process that challenges, not only the way drugs are developed but also how health care practice is delivered, and this has a series of associated social, economic, political and ethical dimensions which we will explore along the thesis. This thesis argues that PGx is a radical innvovation because of the following:

9.2.2.1 PGx Involves Social Interactions

The introduction of PGx into health care will be shaped by a broad range of factors including the nature of the existing health care insurance and delivery system, public attitudes towards genetic testing, the distribution of knowledge about PGx among the payers, providers and consumers of health care, the characteristics of the regulations and practices regarding PGx and clinical use; the willingness of the industry to invest in these technologies and the public perception of them (Buchanan et al., 2002).

PGx is in general perceived to be beneficial by the lay public who consider that it will lead to better health and disease prevention (Almarsdóttir et al., 2005), although health care professionals are more cautious about its consequences (Nielsen and Møldrup, 2006). Doctors, who constitute the key professional group in the NHS (Ham, 2004), have little evidence of the utility or even validity of PGx in clinical contexts (Webster et al., 2004), an important disincentive for its use in this context. Health care personnel need further education on how genetics will change working procedures, while a more widespread use of genetic testing will increase the knowledge of individuals about their own genetic backgrounds and will encourage the lay public to become more demanding in terms of genetic tests (Nielsen and Møldrup, 2006). In parallel to the rise of social awareness, there is a need for dialogue among the stakeholders within society in order to develop criteria regarding how the use of genetic and all medical information should occur (Lindpaintner, 2003). At present, these debates are very much dominated by the research and clinical communities, through networks of collaboration, publications and contributions to policy debates. However, the broad use of PGx is also very much surrounded by professional scepticism (Hedgecoe, 2004).

9.2.2.2 PGx is Technically Complex

Drug response involves dozens to hundreds of genes and it implies a mechanism of absorption, distribution, metabolism and excretion (ADME), as well as interactions with endogenous and exogenous factors (Flordellis, 2005), so even accurate PGx information might have limited value (Webster et al., 2004).

It is also questionable whether there are enough genetic variations in drug responses among individuals to make genetic testing worthwhile. If more than one gene is involved in a drug response, PGx will be more complex and less definitive, and this, in addition to the difficulty of predicting the consequences of environment over drug response, may make it complicated to extract definitive conclusions on the value of PGx drugs (Buchanan et al., 2002). So there is still a need for prospective data on the clinical outcomes of pre-genotyping treatment (Gardiner and Begg, 2006, Shah, 2006); otherwise, the associations of phenotype-genotype would not be sufficiently robust.

9.2.2.3 PGx is Economically Challenging

PGx emerged as a new industrial sector to exploit the opportunities promised by the new technology that emerged from the Human Genome Project. Two types of companies were involved in the development of this: small biotechnology firms dedicated to creating "platform technologies" for the genetic analysis of drug response; and big pharmaceutical companies specialising in marketing blockbuster drugs. PGx has offered opportunities for drug and diagnostic companies to create business partnerships as an integrated strategy for co-developing diagnostic products and PGx treatments (Arnold and Hall, 2005). This has required an exchange of ideas and skills (Bukaveckas, 2007). In fact, some companies investing in PGx have started preparing for the impact of the technology by collecting DNA samples from participants in their clinical trials. But furthermore, PGx involves association studies that link genetic mutations with drug response and for this, expensive research is needed (Goldstein, 2003). Therefore, investing in PGx is not free from a high degree of risk and a high level of uncertainty and the probability of market failure if drugs are not successful enough might force the industry to conclude that large expenditure on regulatory processes and R&D would not be justified by the added benefits of PGx.

9.2.2.4 PGx has Regulatory Implications

The implementation of PGx and the co-development of drugs and tests faces a series of regulatory issues (Melzer, 2003):

- There are conflicts between the need to share genetic data and the need that companies have to ensure patent protection and market exclusivity, for which data needs to remain confidential.
- There are uncertainties as to how to regulate the diagnostic tests associated with new drugs. It is not yet clear whether the IVD Directive will require evidence of clinical validity and utility (the capacity to detect a particular disorder and its benefits when introducing it into clinical practice) or whether it might just require analytical validity (a measure of the accuracy and reliability of the test) (Melzer, 2003). It is not clear either if the IVD Directive will be made a mandatory part of decision-making, setting the rules to identify and select patients according to their genetic and/or phenotypic biomarkers associated with drug response (Arnold and Hall, 2005).
- The lack of regulations on both commercial diagnostics and laboratory developed tests impacts on the lack of standards for testing, which risks adversely impacting public health care (Hudson and Javitt, 2009).
- At the moment there has not been a clear evaluation of the tests offered by laboratories. Regulatory authorities currently cover commercial testing kits but not non-commercial tests (or laboratory developed tests, known as LDTs or also "home-brew" tests) (Buchanan et al., 2002).
- Post-marketing surveillance systems for drugs need to investigate the PGx causes of ADRs, especially severe ones; however, health care professionals have little incentive to contribute to the clinical performance of tests undertaken with marketed equipment.

9.2.2.5 PGx has a Political Dimension

Medical technology has created a range of very different problems, such as how to contain the costs of technological innovation, how to ration the benefits of innovation and how to regulate the risks of innovation. These problems are not new, although the political environment in which they have emerged, is (Moran, 1999). For this reason, analysing PGx

innovation requires an understanding of the socio-political environment in which it emerges and is produced. The difficulties that are raised by the introduction of pharmacogenetics into practice indicate that there are existing gaps between the intentions of policy-makers regarding to what the introduction of the new technologies refers, and what happens in practice (Klein, 2001). The introduction of new PGx treatments in the NHS is driven by the National Institute of Clinical Excellence (NICE) which sets guidance on the basis of clinical utility and cost-efficiency, but also depends on how individual treatments are accepted at a local level (Ham, 2004), but often there are divergences between national aspirations and local service delivery mechanisms.

9.2.2.6 PGx Faces New Ethical Issues

Ethical debates about PGx often conclude that genetic tests involve exceptionally serious ethical concerns that require novel ethical principles (Buchanan et al., 2002). However, in the case of PGx, not always new but stricter ethical frameworks are needed. Some of the current measures to protect confidentiality involve: the availability of patient counselling; increased patient knowledge about genetics; the physician's understanding of the need to keep the results confidential; the establishment of codification strategies that act as firewalls and control access to genetic information; and the establishment of specific legislation that prohibits insurers and employers from discrimination (Buchanan et al., 2002). However, stricter ethical arrangements are needed, for example to assure the long-term confidentiality of patients that undergo clinical trials or genetic testing.

9.3 Entry of Pharmacogenetics into the Clinic – A Diffusion Process

The controversies and uncertainties that currently hamper the widespread use of TPMT and EGFR testing in the clinic as well as PGx in general, relate to a broad range of factors: social, technical, economic, ethical and political, which, despite having different natures, are heavily intertwined. Drugs, diagnostic tests, biochips, mutation analysis kits, DNA sequencers, together with the reagents, laboratory equipment and other associated genetic services necessary for PGx analysis, are all technical artefacts aimed at improving health service delivery mechanisms. However, although these technologies contribute to PGx development and to technical progress, their translation into a clinical setting requires a deep understanding of the specific socio-economic context in which they are embedded.

So, even though PGx aims to improve drug therapies, adjust drug doses, avoid ADRs and, in general, optimise patient care through better drug management strategies, such targets cannot be reached unless PGx technology adapts to the particularities of the health care system in which it is hoped to be implemented, as well as to the regulatory system that controls it. This adaptation requires mutual interaction and the establishment of feedback mechanisms (e.g. after drug approval, clinicians, manufacturers and regulatory agencies engage in a process of post-marketing surveillance, where any anomaly with the marketed drug needs to be reported by the clinician to the regulator and then the regulator will establish which action the manufacturer needs to take on the drug). In this way, the drug is being co-shaped by a set of actors and a set of events occurring between users, producers and regulators.

These co-shaping mechanisms aim to overcome the present gaps and ongoing controversies that hinder the widespread use of PGx in the clinic, to look for new strategies, regulations, forms of practice, organisational changes or institutional re-arrangements that facilitate the inclusion of PGx in the structures that control service delivery.

9.3.1 Diffusion of Innovation in a Highly Regulated Sphere

One of the most important characteristics of medical innovation, which differentiates it from other types of innovation, is that it is highly regulated, both when it reaches the market and at the point of service delivery. Drug regulatory agencies need to grant market approval for drugs, tests and medical devices and then grant permission for their implementation in the health system. For this reason, medical technologies do not reach a state of maturity until they bridge the existing regulatory gaps.

In the UK, the National Institute of Clinical Excellence (NICE) is an important rationaliser of medical treatments. It emerged in 1999 to provide evidence-based guidelines through health technology assessments and cost-effectiveness studies and, currently, the implementation of innovative drugs and technologies is controlled by NICE (through its clinical guidelines) and NHS Trusts are heavily bound to them. However, since NICE cannot appraise every single technology and drug on the market, NHS Trusts have certain margins for manoeuvre in cases where there is not a specific NICE guideline, such as in the case of TPMT testing.

NICE recommendations influence medical practice, although clinicians also make assessments based on their knowledge, their peers' opinions and the NHS Trusts they belong to. Clinicians can take particular actions according to the recommendations of their peers about what has been published in the literature, their personal experience and what the NHS Trust allows them to do. However, sometimes, disparities between what the NICE guidelines advocate and what the clinical professionals believe is clinically relevant, create conflicting situations. In cases like this, the role of clinical associations is crucial as they provide informed opinions, although sometimes these are also conflicting. This is illustrated in the case of TPMT testing. TPMT testing has not been appraised by NICE and, as a consequence, since its implementation is not compulsory in the NHS, some NHS Trusts have established TPMT pre-screening policies and others have not. Some clinical associations claim that TPMT testing should always be implemented and other do not. There are, therefore, apparent disparities in perceptions about the benefits of TPMT testing even among the clinical community and this is blocking the development of a clear guideline applicable across disciplines.

Despite the fact that NICE guidelines are strong drivers for technology adoption, clinical associations also release professional guidelines that have a great degree of influence over the clinical community since one of the drivers for clinical practice is peer opinion. For this reason, professional guidelines are sometimes as influential as NICE guidelines and can be very influential in areas not covered by NICE guidelines. An example of this is TPMT testing in dermatology. Dermatologists, by publishing a guideline that recommended the use of TPMT testing (Anstey et al., 2004), extended its use across the specialty, so that now all dermatologists in the UK pre-screen their patients before starting treatment with azathioprine (respondent 12). Also, the dermatology guidelines have been influential over other clinical specialties (e.g. rheumatology), resulting in an increasing demand for TPMT testing by rheumatologists (Payne et al., 2007).

TPMT testing is not the only case that has adjusted to this conflicting pattern. There are a number of drugs and technologies that, because they are off-patent and rather cheap (since they are subject to competition from generics), are not subject to NICE's appraisals. NICE prioritises technology appraisals of drugs and technologies likely to have a significant impact either on improving health outcomes or reducing costs. However, what is understood to be a significant health outcome is also subject to interpretation. The NICE selection criteria have raised significant criticism from the clinical community, the private

sector and patient organisations, who believe that it neglects the clinical importance of other drugs. For instance, it seems not to be prioritising appraisals of drugs that have been on the market for a long time or those that target a small number of patients (or diseases that have a "small market" such as rare conditions, which affect no more than 5 in 10,000 people). On the contrary, it often appraises drugs that have just entered the market. This often generates tension among manufacturers, practitioners and patient groups, as has been illustrated in the case of Tarceva®.

9.3.2 The Convergence of Product and Process Innovation

The innovativeness of PGx and personalised medicine relies on the fact that they can both lead to more targeted therapies, based on the results of genetic and phenotypic analysis, implying new ways of diagnosing disease, new forms of interpreting clinical results and new approaches for treating patients. PGx can, therefore, lead to new drugs (Attar and Lee, 2003) as well as to new ways of offering health care services and reducing adverse drug reactions: it is not only a product but also a process innovation. According to OECD definitions, a product innovation is the introduction of a good or service that is new or significantly improved with respect to its characteristics or intended uses. Process innovation is the implementation of a new or significantly improved production or delivery method which includes significant changes in techniques, equipment and/or software (OECD, 2006). Product and process innovations are, then, different, although interdependent, because as new product features are agreed by producers and customers, and as a market expands, there is a shift in which product and process innovations occur. As the rate of product innovation increases, it is common to observe an increase in process innovation that affects the characteristics of products, processes, competition and the organisation as a whole (Utterback, 1994).

As the business cube (see Figure 9.2) shows, a new generic technology, new markets and new processes, bring with them the need for radical change within a company, and probably an entire reorganisation into a new form of company oriented towards a new business field (as shown by the arrow). So, it is expected that, as new gene-drug associations are discovered and, as new technologies such as sequencers and other forms of genetic screening emerge, drug development strategies will need to include these technological elements in their processes. Improvements in drug delivery will then require a shift towards new business models.

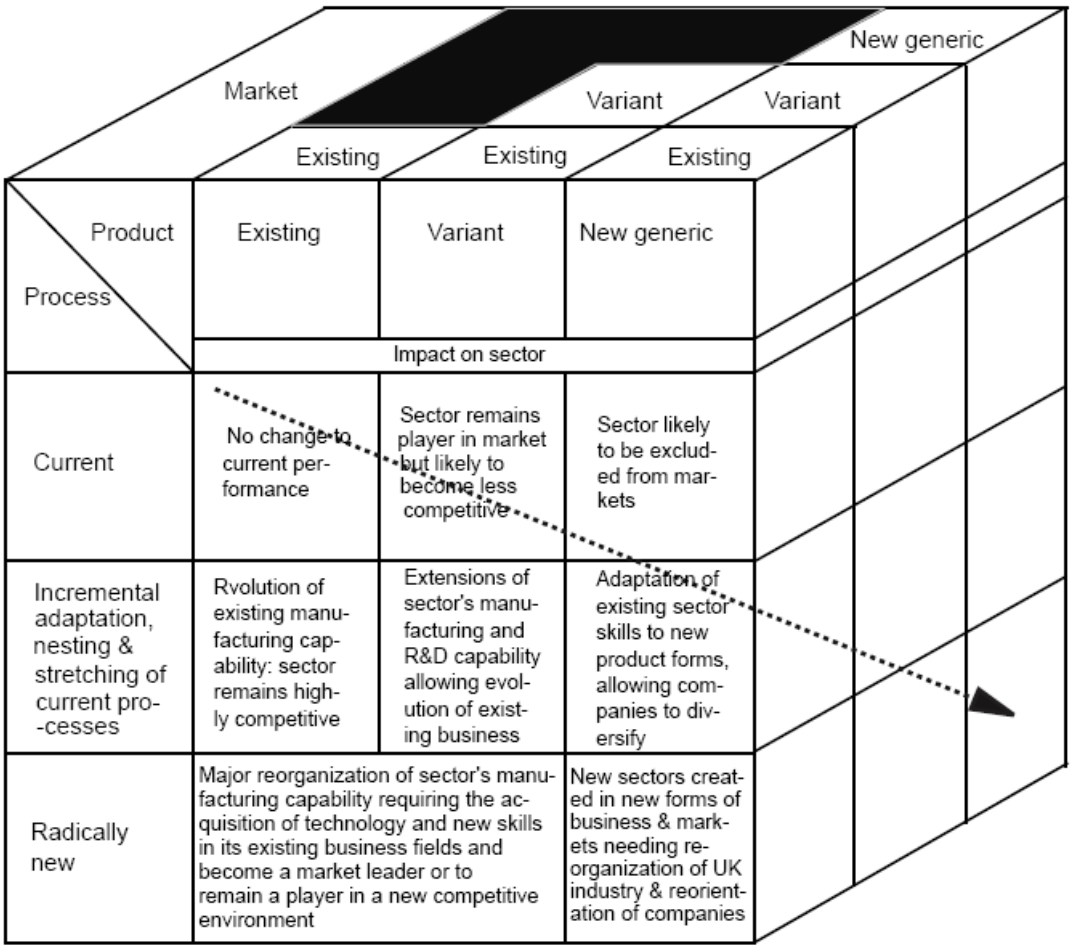

Figure 9.2: Business Cube (Loveridge, 2008)

It is still uncertain how PGx will develop. At the moment, some pharmaceutical companies are interested in co-developing drugs and tests, although these are in a minority. In the future, with more understanding of genetics, it might be possible that the development of "Minibusters" will grow and the "blockbuster" model of drug development will shift into a "Minibusters" model. However, the way in which this may happen will depend on the availability of biomarkers of drug response, on the interest of private companies in including these biomarkers in drug development, on the regulatory mechanisms and on the acceptance of these new drugs by clinicians and patients.

Similarly, the implementation of PGx services will imply organisational changes in health care practice. Clinicians and pharmacists will need more genetic skills, laboratories will need to upgrade their technologies, and pharmaceutical companies, together with regulators, will need to define strategies for post-marketing surveillance, not only for new drugs but also for the accompanying diagnostic tests. In general, the introduction of PGx

will require better coordination among the actors involved in service delivery. However, a model has not yet been developed that is able to re-define these relationships.

PGx innovation goes beyond the development of technical devices such as drugs, diagnostics and the like. The inclusion of these into a health care setting implies a shift in the current delivery processes. New products are accompanied by new regulations, clinical guidelines and forms of practice; they require a different approach to the patient and different ways of understanding clinical practice. Therefore, the inclusion of medical innovation into health service delivery needs of new professional interactions and a change in the ways in which health organisations operate.

9.3.3 Organisational Implications

The heterogeneity of the factors that influence the adoption of PGx and personalised medicine makes it almost impossible to explain their use and their implications without understanding the context in which they occur, because technological innovations do not only reside in artefacts but also involve changes in market relationships, as well as having other organisational implications (Miles, 2005). The implementation of PGx services needs to acknowledge that any medical innovation emerges under an organisational dimension that will facilitate or hamper its translation into the clinic.

PGx and the implementation of drugs and tests in clinical practice also face organisational implications, because using new diagnostic devices and prescribing drugs according to the results of diagnostic tests (as opposed to other clinical assessments) requires the establishment of, not only testing facilities, but also closer interactions between the clinicians who prescribe the drugs and the tests, the laboratories that do the testing, and the pharmacists who need to adjust the prescriptions according to the results of these tests. Therefore, clinical decision-making in PGx would require coordination between physicians, pharmacists and PGx laboratories and hospitals will need to realise this and adjust their governance mechanisms to the needs of PGx and personalised medicine.

In a recent review, innovation in health service delivery organisations was defined as a set of routines and ways of working that are directed at improving health outcomes, administrative efficiency, cost-effectiveness, or users' experiences, implemented by planned and coordinated actions (Greenhalgh, 2001). These actions relate to the mechanisms that the health system needs to put in place in terms of biomedical research,

drug development activities and manufacturing processes, in order to deliver new or improved clinical services.

Organisational innovation refers to the implementation of a new organisational method in the firm's business practices, workplace organisation or external relations (OECD, 2006) and this implies the creation or adoption of an idea or behaviour new to the organisation. The innovativeness of organisations (such as health care services) depends on how new services are set up, and how the organisation handles the adoption of new roles, new skills, and new interactions associated with these new services.

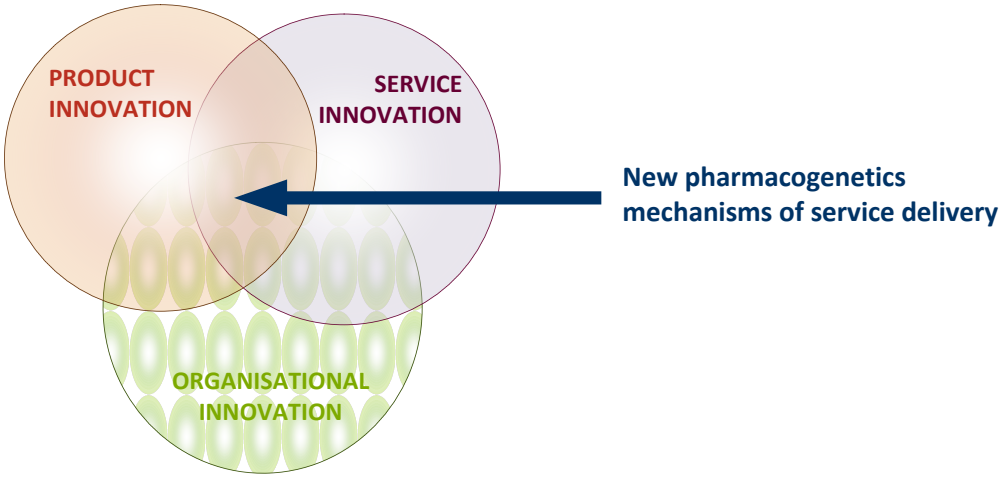

Figure 9.3: PGx new mechanisms of service delivery defined as the intersection between PGx product, process and organisational innovation.

These organisational changes also involve the reconfiguration of the market for traditional drugs, the development of new business models and the acquisition of new firm strategies, all of which results from the exploitation of a new mode of knowledge production (*mode2*), in which collaborative approaches between universities, research centres and industry facilitate the exchange of knowledge, and a boost of scientific production and technological innovation (Gibbons et al., 1994). This model entails a closer connection between researchers in public institutions and industry (e.g. collaborations between biotechnology and pharmaceutical companies in the co-development of drugs and tests).

Thus, PGx has an organisational component through which product innovations emerge to be later translated into service delivery. Therefore, the emergence of product and process innovations cannot be understood without considering an organisational component that defines the conditions under which new mechanisms of service delivery arise.

Throughout this thesis we will consider that the provision of new health delivery services associated with new PGx and personalised medicine, will lie in the intersection between product, process and organisational innovation, as is illustrated in Figure 9.3.

9.3.4 Feedback Mechanisms among Users and Producers

As was mentioned in Chapter 2, technological change in medicine is not a linear process. It occurs through a series of feedback mechanisms by which users and producers negotiate and re-shape the use of the technology (Gelijns and Rosenberg, 1994). These mechanisms are triggered when the early adopters of a technology (or the lead users) adapt the technology for their particular needs and circumstances, which starts the process of re-shaping (Von Hippel, 2005). These first steps of adaptation help overcoming the initial barriers that a new technology encounter and, once these are overcome, the adoption of the technology increases exponentially until it matures and it becomes widely used.

In the case of TPMT testing, we can highlight two groups of early adopters. In first place, the community of dermatologists, which recommended TPMT testing in their professional guidelines, after which TPMT testing became common practice among this community of professionals. In fact, no dermatologist could take part in the TARGET study as any dermatology patient treated with AZA would be tested for TPMT levels and therefore could not be randomised for the trial. The other group of early adopters was constituted by the TPMT reference laboratories, which set a TPMT testing service nationwide, on the assumption that TPMT testing was highly beneficial and it could be offered through the NHS at a reasonable price.

The early adopters in Spain were different. Since there were no professional guidelines that advocated for the use of TPMT testing, neither a national strategy that aimed at improving the use of pharmacogenetic information in clinical care, UCB Pharma, with the help of a university laboratory, took the lead in the provision of TPMT testing services.

There were notable differences in who promoted TPMT testing in both countries (due to different national priorities). However, in all cases, the rationale for an early uptake of the technology responded to an anticipation of a benefit from TPMT testing.

In the case of Tarceva® and EGFR testing, there were no early adopters of the test (apart from the research laboratories that were using the test for research use only), because

EGFR testing was not approved for clinical service delivery. In this case it becomes more reasonable to talk about early adopters of Tarceva®, which were, mainly, different groups of lung physicians together with individual clinicians who foresaw the benefits of this new drug and defended (and used if the NHS reimbursed its cost) its widespread use as a first line therapy (and not as second or third line as NICE guidelines indicate) for non-smoker NSCLC patients. The claims made by these groups and of physicians, who actually had the experience in prescribing the drug and seeing its effects (some of them had even taken part in the clinical trials) were also supported by other patient advocacy groups such as Cancerbackup and the Roy Castle Lung Cancer Foundation

9.4 Patterns of Innovation for TPMT and EGFR Testing

9.4.1 AZA, 6-MP and TPMT Testing: Patterns of Diffusion for Off-Patent Drugs

Some bodies of opinion anticipate that PGx is going to have a major impact for drugs under development than for licensed drugs (Human Genetics Commission, 2002). However, TPMT testing exemplifies a case where PGx and personalised medicine can improve the efficacy of licensed drugs. One of the particularities of TPMT testing, which may differ for other and future PGx applications, is that it prevents some of the ADRs caused by AZA and 6-MP, both of which are off-patent (they were first licensed in the 1950s). The fact that AZA and 6-MP have been open to generic competition since their first patents expired, made it reasonable to think that, at least in principle, there was not much commercial interest in investing in a test that was going to prevent adverse reactions to drugs that are open to the competition of generics and are rather cheap - the cost of the test might surpass the cost of the drug. This assumption set the ground for the analysis of how innovation and diffusion of TPMT testing has occurred in the UK.

Invention and Innovation for TPMT testing was triggered in the UK by the reference laboratories, who, with the support of public funds, set up a national service. These laboratories succeeded to develop a technique to measure the levels of TPMT in the blood and to test, only in some cases, the mutation status of some of the genes implicated in the response to AZA and 6-MP. With the set up of these techniques and the dissemination of the information among clinical circles, these laboratories generated a demand for the test,

in particular in dermatology, where the clinical association recommended its use. However, NICE (one of the major actors involved in clinical implementation and reimbursement policies), never appraised TPMT testing, on the grounds that there were other, more expensive and priority treatments and, although the test was proved to be cost-effective (Marle et al., 2006, Dubinsky M C et al., 2005), TPMT testing was not included in any of NICE´s clinical guidelines. However, despite this fact, the demand for testing increased in the UK (Ford et al., 2004a, Ford et al., 2004b, Birmingham City Hospital, 2009), even though there was not yet a public agenda that recognised the importance of preventing ADRs caused by AZA and 6-MP through TPMT testing.

One of the conclusions that came out of the TPMT case study pointed out that, while NICE (through its clinical guidelines) is a strong driver for adoption (its guidelines are mandatory), when NICE does not appraise a particular technology and does not release a specific guideline, there are other elements that influence innovation diffusion. These other elements, in the case of TPMT testing, have been: the reference laboratories and the clinical associations and NHS Trusts that have decided to do TPMT testing on the basis that it improves patient care and avoids severe ADRs.

Also, the fact that two public laboratories have taken the lead in the UK and are offering TPMT testing services, demonstrates that:

- Expertise in product and service innovation in PGx and diagnostic testing is not exclusive to the diagnostic or pharmaceutical industry. In the case of TPMT testing, this has been accentuated by the fact that there is not a formal recommendation across the NHS that encourages the pre-screening of diagnostic testing for licensed drugs, such as azathioprine.
- The case of TPMT testing shows that, in the UK, the implementation of PGx for preventing ADRs to licensed drugs is strongly driven by lead users who reside in public hospitals, whose home-brew tests do not comply with the requirements of the IVD Directive and are not subject to commercial application.
- Innovation in service provision is heavily dependent on the demand for testing in hospitals and on clinical acceptance (Anstey et al., 2004, Payne et al., 2007).
- The definition of a market in PGx goes beyond the frontiers of the pharmaceutical and diagnostic industry. The implementation of PGx is the result of the interactions between a series of actors, from the public and private sectors, all of whom shape

the use of the technology. If we understand the market for PGx as the demand for a specific service, then pharmaceutical and biotechnology companies are as much involved in the process as public laboratories in NHS hospitals.

- The lack of protection for home-brew tests against competition from private companies could threaten public service provision if other commercial alternatives emerged. Similarly, as is already occurring with the Myriad BRCA1, commercial alternatives may compromise public provision of breast cancer screening provided by some European laboratories.

In Spain, the context in which TPMT testing is offered differs from the UK. The main driver for UCB Pharma in promoting PGx, was not so much avoiding ADRs as re-launching azathioprine as a more innovative drug that would have a PGx component and therefore an added value that would, presumably, increase drug sales and position the drug as a strong competitor to newer drugs on the market, such as Cellcept®. For this reason, UCB Pharma (and not a public laboratory) was interested in changing the technical specifications of azathioprine, in order to improve its competitive advantage against the newly launched Cellcept® (Roche). This was a major difference between the strategies adopted to promote TPMT testing in the UK and Spain. While in the UK there was no private commercial interest behind the use of TPMT testing (although the services, in particularly in the Birmingham laboratory, were run in a rather entrepreneurial fashion), in Spain, UCB Pharma aimed to develop a TPMT testing service that could improve, not only the safely, but also the sales of azathioprine.

9.4.2 Iressa®, Tarceva® and EGFR Testing: Patterns of Diffusion for Drugs under Development

The cases of Iressa® and Tarceva® illustrate the second of the technological trajectories described in chapter three: PGx to improve drug response. As we have seen in chapter 7, although, neither *Iressa®* nor *Tarceva®* are described as PGx drugs yet, in the future they may be delivered in association with a genetic test, provided there is further evidence of their clinical utility. The co-development of drugs and tests, in this case, is an example of the possibilities of using PGx for improving the efficacy of licensed drugs as a business-driven strategy to widen the indications of *Iressa®* and *Tarceva®* and position them within the large market for lung cancer therapies.

Taking into account that the response to both *Iressa*® and *Tarceva*® may be susceptible to mutations on the EGFR gene, in the future, both drugs could benefit from co-development with a diagnostic test: *Iressa*® could be reintroduced into the UK market under certain genetic conditions and *Tarceva*® could obtain wider NICE approval if it was proven that EGFR mutations/amplifications affected drug response considerably. If such situations occurred, both Iressa® and *Tarceva*® would need to be prescribed only after a genetic test had given results showing EGFR mutations/amplifications.

The outcome of co-developing either *Iressa*® or *Tarceva*® with a PGx test would be similar in both cases: targeting the drug to "good respondents" to improve drug response. However, the means used to achieve such an outcome would be different for each of them, because the nature of the manufacturing companies (Roche and AstraZeneca) is different. Roche, who manufactures *Tarceva*®, is a large pharmaceutical and diagnostic company; it has previous experience in PGx (it was involved in the co-development of the HER2-Herceptin drug/test, one of the first commercial PGx applications) and, if *Tarceva*® was to be co-developed with a test for EGFR, there are chances that the same company would develop both drug and test. The situation at AstraZeneca, who developed *Iressa*®, is different. AstraZeneca is not in the business of diagnostics so, if *Iressa*® was ever to become a PGx drug, it is likely that another company would have to develop the genetic test associated with the drug. In this case, DxS, a small biotechnology firm funded by ex-AstraZeneca managers and who owns one of AstraZeneca's diagnostic technologies (such as the Amplification Refractory Mutation System - ARMS™) and had previously established collaborations with AstraZeneca, could be a candidate. DxS already has some EGFR testing technologies on the market, selling them mostly in the US and Japan. However, other companies who are also working in the area of diagnostics may also be candidates.

However, before any drug-test development takes place, it is necessary to identify the exact mutations that affect drug response. At the moment there are numerous mutations identified on the EGFR gene but not all of them influence drug response. Besides the mutations on the EGFR gene, response to Iressa® and *Tarceva*® has another phenotypic component: both drugs work better in Asian females' never-smokers. For this reason *Iressa*® and *Tarceva*® continue to be used in Japan, where they are both approved as second line treatments.

The fact that *Iressa*® and *Tarceva*® are prescribed differently in the UK and in Japan, indicates that innovation is globalised but diffusion is local, since it is highly constrained by local regulatory arrangements.

Recent publications advocate *Iressa*® to be as effective as chemotherapy (ScienceDaily, 2008), a statement that may be influential in the future use of *Iressa*® worldwide. In fact, following these events, in November 2008 NICE announced, for the second time, a new appraisal of *Iressa*® (NICE, 2008c) to evaluate the cost-effectiveness of the drug in the treatment of NSCLC. The first results of this appraisal are expected to appear in May 2009. After all the technical data has been gathered this, again, may change the current regulatory regimes that control service delivery for NSCLC in the UK.

Some of the conclusions we can extract from the *Iressa*®, *Tarceva*®, and EGFR testing case are the following:

- NSCLC, as with all other types of lung cancer, does not yet have an effective cure and has very low rates of survival (just over a year). For this reason, the pharmaceutical industry is interested in developing innovative therapies for NSCLC, as well as because it affects more than 1.2 million patients a year, causes 1.1 million deaths annually, 500,000 in the US, Europe and Japan, and had a market worth an estimated US$3.7 billion in 2006. In addition, the addressable NSCLC market is expected to increase by 17% by 2012 (Espicom Business Intelligence Ltd, 2007), which makes NSCLC an attractive target for the drug industry.
- The interest in EGFR testing lies behind the need to look for "good respondents" in the UK so that *Tarceva*® can be widely used there, *Iressa*® can be re-introduced onto the market and both *Iressa*® and *Tarceva*® can extend their current indications from third/second line treatments to first line treatments in Japan and other regions of the world.

9.5 TPMT and EGFR Testing – A Macro Level Analysis

This section is aimed at answering the last of the research questions: "How the controversies around TPMT and EGFR testing may be generalised to a higher level of policy analysis, which informs policy decisions on how PGx service delivery might be implemented

in a public health care system such as the NHS?" This section will address general issues common to the cases of TPMT and EGFR testing, mainly ethical and regulatory, which can potentially be extended to other PGx applications. The legal, ethical and regulatory aspects explained in the following sub-sections will be addressed from the perspective of public health service delivery.

9.5.1 Patents and Public Service Delivery: Legal Aspects

A genetic sequence can be patented once its function is known. When this happens, that genetic sequence is treated as an invention and not just as the result of scientific discovery. Consequently, patented genetic information is not treated as a public good but as a commercial product. This raises several concerns:

- There is an ongoing debate about whether genes should be considered as discoveries or inventions, with an extensive body of opinion (represented by the research, the clinical and the patient community) that is against the definition of genes as marketable products. It is arguable whether commercialising with DNA sequences is ethical and whether genetic information should be treated as a private good.
- A patent must be novel, inventive and have industrial applicability; however, it is arguable whether genes are patentable entities since they are not inventions but discoveries, as set out in Art. 52 to 57 of the European Patent Convention (EPC) (European Patent Office, 2007).
- The European Patent Office (EPO), unlike the US Patent and Trade Mark Office (USPTO), allows democratic control over patenting. Any patent can be appealed within 9 months of the granting date, but Europe lacks a system that ensures the guidance and surveillance of genetic inventions.
- Any genetic information which has been patented is marketable and cannot be exploited and used by anybody other than the patent holder. This also prevents public researchers and service providers from doing further research on that gene or from offering an associated genetic service. For example, if a company patents a test for TPMT it could limit the two UK reference laboratories who are currently the main service providers.

- The final aim of patents is to obtain a commercial gain. It is arguable, however, whether it is ethical to obtain a commercial profit from genetic sequences, which are not inventions but part of the biological constituency.

9.5.1.1 Patenting Diagnostic Tests – "Home-Brew" and IVD Tests and the Influence of Pricing Differences

Patent protection is a strong driver for private companies to develop In-Vitro Diagnostics (IVDs) (in opposition to "home-brew" or laboratory developed tests - LDTs) (Hogarth and Melzer, 2007). However, one of the fears about patenting genetic tests is that it might give access to genetic testing (Matthijs, 2006), with an associated risk of limiting access to the service to whoever is willing to pay. As mentioned in the previous section, patents protect the innovation by preventing competitors from doing a similar type of activity. As a result, the service provision offered in public clinical laboratories, which run their own in-house tests because they cannot afford the associated costs of clinical trials and patenting, may be at risk.

A series of issues of concern emerge from this (Matthijs, 2006):

- Article 52 of the EPC of 1973 says that "methods for treatment of the human or animal body by surgery or therapy and diagnostic methods practised on the human or animal body shall not be regarded as inventions" (European Patent Office, 1973). It is unknown why this was not updated to include genetic testing.
- The aims of the patenting system, which are the promotion of innovative research and progress through the generation of useful new products, are not necessarily met in the case of gene-based diagnostic methods, since patents interfere with the availability of genetic tests for the patient.

The first genetic patent granted to Myriad Genetics illustrates some of the consequences of gene patenting over public service delivery. The case of the BRCA genes illustrates the strong influence of IPRs over genetic testing, not only in the development of new diagnostics but also in service provision. Under the current legal framework, gene patenting not only increases prices but also reduces access to public PGx services.

9.5.1.2 "Home-brew" and IVD Tests: Pricing Differences

As genetic tests emerged, public laboratories increasingly introduced them into routine monitoring in the form of "home-brew" tests. Later on, as new markets have developed, pharmaceutical, biotechnology and diagnostic companies have started to invest in them, in order to create commercial IVDs. Therefore, the main instigator in the shift from "home-brews" to IVDs is commercial.

Public health care systems such as the NHS are likely to favour the use of "home-brew" tests (where available), instead of commercial IVD tests, because the NHS cannot reimburse every treatment available on the market and "home-brew" tests are cheaper since they do not have the associated costs of doing clinical trials and patenting. An example of the pricing differences between "home-brews" and IVD tests is illustrated in the case of TPMT testing. Although they are not commercialised in the UK, the US company, *Prometheus* offers two commercial tests for TPMT testing (phenotyping as well as genotyping) at an approximate cost of $300 each (Prometheus, 2006). In the UK, the reference laboratories charge for a TPMT PGx service (which includes phenotyping and, where needed, also genotyping) at an average cost of £25- to £30 per test (Birmingham City Hospital, 2009).

9.5.1.3 Avoiding Testing Monopolies and Enhancing Good Practice

The development of "home-brew" tests is particularly important in conditions where there is not enough of a market to justify commercial development (e.g. PGx for generic drugs or orphan drugs). In cases like this, private companies are not likely to invest in a commercial IVD test because there would not be enough of a market for it (Hogarth and Melzer, 2007). However, while the provision of "home-brew" tests might be relevant in these cases, as was explained in the discussion and in the above sections, they are not sufficiently regulated either at the point of development, or at the point of delivery. Because of this, in order to enhance the benefits of "home-brew" testing and also, to benefit from the use of commercial IVD tests in clinical practice, it is necessary to strengthen the current regulatory system and establish delivery mechanisms driven by clinical utility and good medical practice that will apply to both commercial and non-commercial tests (such as the implementation of genetic counselling as a necessary condition for delivering testing services). At present there is not a body such as NICE that evaluates the feasibility of offering a "home-brew" test as opposed to a commercial diagnostic, but, as more

diagnostic tests become available, it may be possible that other mechanisms that rationalise the use of diagnostics, in the same way that NICE does currently with new drugs, will become necessary.

9.5.1.4 Controversies Surrounding IPR, Gene Patenting and Service Delivery

Patenting is a form of protecting innovation. However, patenting genes has always been contested. Anyone can be granted the patent of a gene, provided the function of that gene is known (not all the genetic functions are known). Similarly, anyone can patent a genetic test, which also confers on them the rights of exploitation of the particular genetic sequence the test targets.

Patenting and granting market exclusivity for genetic tests means that, nobody else can exploit that same genetic sequence. The controversy emerges when public service providers that were already using that genetic sequence, might be asked by the patent holder to stop offering the service because they hold market exclusivity.

9.5.2 Ethical Issues of Diagnostic Testing

The use of genetic data and its disclosure raises various ethical considerations, in particular relating to who will have access to genetic data once such services are implemented in the clinic. Many of these ethical considerations stem from:

- The fear of gene sequences being owned by private companies.
- The possibility of developing expensive diagnostic kits that are not available to everyone.
- The right of access to any personal genetic information and how the disclosure of such genetic information will be regulated.

9. 5.2.1 Disclosure of Genetic Information

Article 8 of the European Convention on Human Rights states that: *everyone has the right to respect for his private life* (European Court of Human Rights, 1985), and this includes the right to be protected from the unwanted publication or disclosure of personal medical data, such as genetic information. However, any personal information may be disclosed if it prevents injury or damage to health and, according to this, disclosing the results of genetic

tests would only be justified if it implied the avoidance of risk, although this is often not the case. The arguments around data protection are still debatable and, while private insurers stand for mandatory disclosure in order to avoid problems of adverse selection, other groups claim legislation should prevent such disclosure (Wilson, 2006). The emergence of genetic testing led to concerns about the use of such information by health insurers. In response to these concerns, the UK Government, in conjunction with the Association of British Insurers, released in 2001 a moratorium on insurers' use of predictive tests, which allows patients who have taken a predictive genetic test to obtain significant levels of cover without disclosing the results of that test. This moratorium will last until the 1st November 2011 (HM Government and Association of British Insurers, 2005).

The genetics moratorium was established on the grounds that genetic information could be divided into diagnostic and predictive genetic tests, although the concept of genetics developed by the European Society of Human Genetics does not differentiate between predictive and diagnostic genetic information. The moratorium covers predictive genetic tests until 2011 and allows patients to obtain significant levels of insurance coverage without the disclosure of their genetic information (UK Government, 2005). However, the moratorium does not cover diagnostic genetic tests which are indicators of disease, especially for single gene disorders. So, while the genetics moratorium was established on the grounds that genetic information could be divided into diagnostic and predictive genetic and does not cover diagnostic tests, the European Society of Human Genetics, in its definition of genetics does not make such a differentiation.

9.5.2.2 Informed Consent, Ownership and Control of Information

Before any patient gives a sample for TPMT testing (as well as for any other types of testing that are not routine blood monitoring), s/he needs to sign an informed consent form in which s/he agrees to give a blood sample for testing. However, often, even after giving their informed consent, patients are not fully aware that they might be giving a sample for a genetic analysis (if TPMT genotyping is required) (respondent 12). After the test is done, the information gathered by the laboratory goes back to the clinician who referred the sample and the patient remains outside the process. Patients do not receive any further notice that informs them whether or not they are TPMT deficient and they might be at risk of an ADR if they are prescribed with AZA and neither are they told that their DNA has been analysed and might be stored for a future use (respondent 1).

At the moment samples are used for specific genetic tests and the fact that they are being stored is not having immediate consequences. However, in the future, these samples may be used for other purposes and it is then when concerns about the ownership and use of these samples may emerge, although the fact that blood and DNA samples are currently being stored indicates that there is a lack of awareness about the implications that the storage of personal information might have in the future.

> *I've got freezers to store the samples. I've got 2,000 samples a day coming in, and we store some of them to look at in the future. That's not a huge issue at the moment (in a public laboratory)…ethically, this has been clarified quite recently in the UK, we are allowed to use the material that comes in, to helps us develop, for example, references and things like that…. (respondent 1).*

Legally, once a test has been done on NHS premises, the owner of such data and the person who has legal ownership over it, and is awarded permission to use it, is the Department of Health (DoH). The DoH eventually allows other people to use such data under strict guidelines, but none of this is known by a patient giving their informed consent for a test (either genetic or phenotypic) (respondent 10).

So, at the moment it is not very clear for the patient whether informed consent implies appropriation of the sample or control of future exploitation of the sample and there is a need to revise how samples are controlled and whether control implies ownership or whether there should be mechanisms through which genetic material could be controlled by the hospital but still owned by the patient (respondent 10).

9.5.2.3 Management of Informed Consent and the Future Use of Samples

In the NHS, patients that undergo specific testing (such as TPMT) need to sign an informed consent form, in which they agree to give a blood sample for testing. Similarly, patients entering clinical trials also sign informed consent forms, agreeing to the legal terms and conditions of the clinical trial.

- In the NHS, once a sample is taken, it can be kept by a laboratory for an undetermined period of time. The uncertainty here lies in whether a patient who has given a sample for routine TPMT testing, for example (and not as part of a clinical trial), is aware of the fact that his/her sample might be used in the future for another purpose. At the moment, NHS laboratories keep biological samples and

there is no regulation that controls their storage and future use. There are also no protocols for informing patients that their samples are being used for something other than that for which they gave their consent.

- The pharmaceutical companies might be stricter in defining the terms and conditions of the informed consent a patient needs to sign before entering into a clinical trial. Companies are very interested in storing samples and obtaining PGx data that may be used in the future for PGx drug development. But, even when patients agree that their samples may be stored, it is uncertain how companies will integrate this data into drug development.

So, while it is clear that informed consent gives rights of exploitation of biologic samples, it is uncertain whether it also confers ownership of personal genetic or phenotypic data.

9.6 Tackling Controversies and Uncertainties: Some Policy Recommendations

This chapter began by looking at a series of controversies and uncertainties that emerged from the case studies, to explain why TPMT and EGFR testing are not widely used in clinical practice. The impact of these controversies and uncertainties has been analysed in the discussion, within the context of the socio-technical system that drives drug development and service delivery. The implementation of PGx in clinical practice will depend on how the current uncertainties, controversies and other related issues are resolved. This resolution faces a complex situation in which the social, technical, ethical and political underpinning factors are tightly intertwined.

For the purpose of the policy analysis, we introduced in chapter four the policy matrix (see figure 4.2). Here, and in order to make linkages between innovation in PGx and policy recommendations, we adapted the policy matrix to the following assumption (see figure 9.4): the introduction of PGx and PGx testing is "difficult even for experts" due to the existing gaps in knowledge, regulations and lack of consensus about its benefits. This is represented in the figure below by boxes with different colours. Even though we assumed that PGx is difficult even for experts, the degree of control over different factors affecting the technology, varies. For this, they have control over some of these fators (this is represented by the green dots); they have partial control over other elements (dots in yellow) and the have no control over the most contested issues (dots in red). Therefore, the

questions "what is feasible?" "What is possible?" and "What is desirable?", will be answered taking into account the level of control of policy makers over PGx.

But, before answering the questions: What is possible? What is feasible? and What is desirable?, we should note that we aim to inform policy decisions on how PGx service delivery might be implemented in a public health care system such as the NHS.

Every policy measure under the heading "what is desirable?" considers that "the desirable" is to implement a PGx service, accessible to patients through a public health system.

The full detailed policy analysis of the factors considered as crucial for the implementation of PGx, is provided in annex 5, although a summary of the key factors for PGx diffusion are provided below.

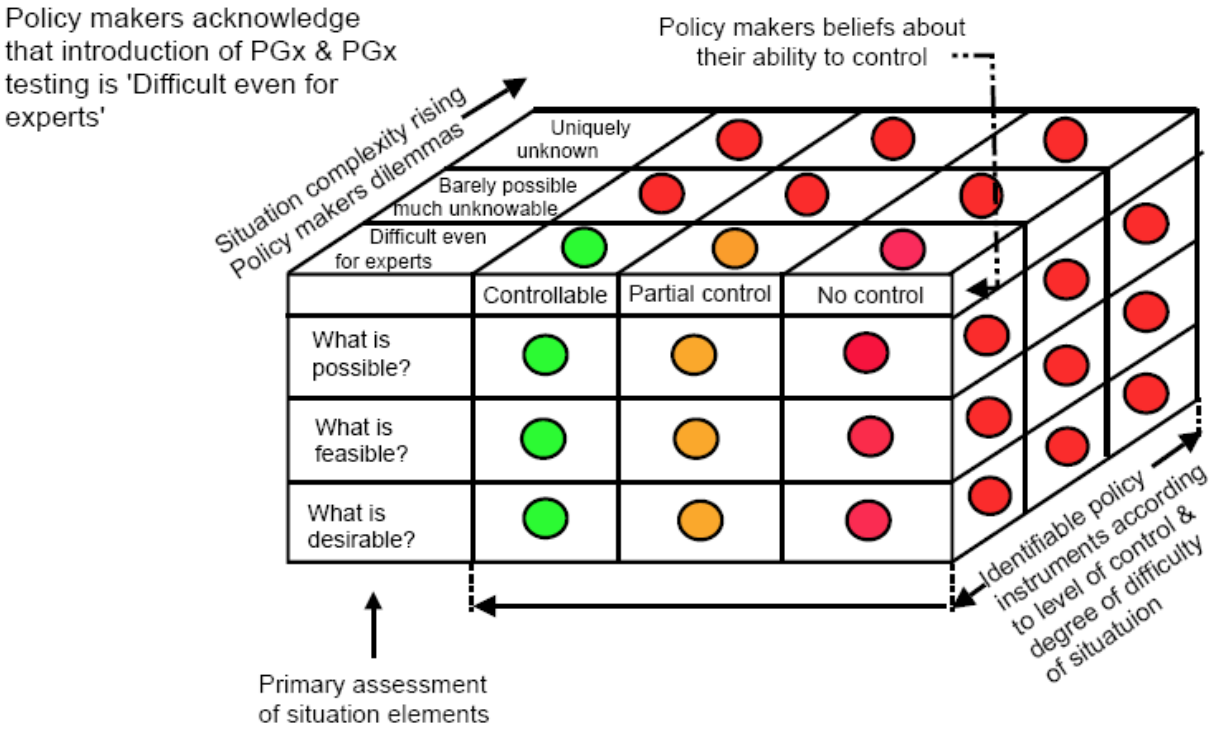

Figure 9.4: Policy Matrix used to study the policy implications of PGx. Adapted from Loveridge (2008)

The following points summarise some of the elements that have arisen during the research and may serve to overcome the existing knowledge gaps and inform future policy decisions on PGx testing:

- The fact that the use of "home-brew" tests is not controlled by the mechanism that control and regulate IVDs, together with the possibility of IVD tests monopolising the diagnostic market and preventing public hospitals from offering similar "home-brew" tests, leads to the urgent need of solutions, whereby diagnostic tests (both "home-brews" and diagnostics) should be implemented on the basis of an optimal analytical validity (or technical accuracy), clinical validity (or its sensitivity and specificity) and clinical utility (potential for improving health outcomes), and not only on the basis that there is a test which is available in a public laboratory or a test has been patented by a private company.
- One of the major points of disagreement in the case of TPMT testing is, the clinical validity of a test that is perceived to be beneficial by some clinical associations but has not been appraised by NICE. In situations like this, where NICE does not appraise technologies, there is an urge to establish frameworks (that go beyond NICE guidelines) that guarantee good clinical practice, in particular when there is a lack of consensus between the actors involved in PGx development and delivery. Also, there should be alternative mechanisms that review drugs and devices not appraised by NICE, in particular, PGx applications and co-development of drugs and tests for off-patent drugs, which implementation, in principle, are not likely to have a huge impact on cost savings, although they may have a high impact on health benefits.
- Under the current patent system, patenting a genetic sequence can lead to a testing monopoly that prevents public laboratories from using the patented sequence either for research or for service delivery (in the form of home-brew test). The establishment of rigorous regulatory frameworks through which public health care systems can maximise the benefits of diagnostic testing either from public or private service providers (e.g. by establishing compulsory genetic counselling that only resides within the NHS and not private companies), could prevent these testing monopolies and could maximise the efforts that public laboratories are putting into developing "home-brew" tests..
- PGx faces numerous regulatory gaps. The lack of a harmonised procedure to approve tests across Europe is one of them. It would be, therefore, desirable to enhance the role of the EMEA in the process of approval of tests. The EMEA or the

national states should also take specific measures that ensure that adequate ethical frameworks for the manipulation and use of genetic information are put in place.

- These elements are inter-dependent and, for the future of PGx service delivery, they should be understood as such. In order to deliver efficient policies that enable the use of PGx testing in a health system like the NHS, it is necessary to acknowledge the implications of PGx testing both, at the point of drug development and service delivery, as well as to understand the interactions and feedback mechanisms that occur among the two. For this, it becomes essential to take a broad perspective of PGx, because testing policies lie in the intersection of all the elements that form the STEEPV acronym. The implementation of PGx into the clinic will depend on the availability of alternative technologies and how pharmaceutical industries, clinicians and regulators favour one or another. In this way it is concluded that policy makers, through the degree of difficulty in the PGx situation, are likely to have only partial control over the continuing emergence of PGx in the clinic.

9.7 General Summary and Contribution

The purpose of this thesis was, first, to investigate the existing barriers that hamper the widespread use of PGx in a clinical setting. These barriers have been presented in the form of controversies and uncertainties (a whole list of controversies appears in annex 5).

In second place and, at the same time as exploring how innovation diffusion and translation from drug development into service delivery takes place, the thesis aimed to prove the following hypothesis (see section 1.2)

- The adoption of PGx requires a re-organisational re-structuring that leads to a new form of service delivery. This hypothesis is widely discussed in chapter 8, where the critical points around PGx at the point of development and delivery are elaborated in detail
- Pharmacogenetics is a radical innovation that challenges the existing norms that rule the existing forms of clinical practice. This hypothesis is answered in chapter 3, which is explicitly dedicated at explaining why PGx is a radical innovation. Chapters 5, 6 and 7, which correspond to the case studies, also provide notions on how PGx

(through TMPT and EGFR testing) challenges the ways of treating patients with 6-MP, AZA or Tarceva®.

- The clinical implementation of PGx depends on elements which, sometimes are driven by certain institutional arrangements, but others, by contingent factors. In chapter 8, section 8.3 is dedicated at explaining what happens when there are no specific regulations for PGx delivery. In that same chapter, section 8.6 deals with the institutional settings in which PGx is embedded. Further in the thesis, chapter 9 dedicates a section (9.3.4) to explain the the process of diffusion through feedback mechanisms among users and producers and, the way in which these feedback mechanisms occur cannot be anticipated.

Finally, the thesis aimed to inform policy on ways of improving PGx service delivery through a public health system. The identification of existing gaps, in particular at a scientific and regulatory/ethical level (see sections 9.5.1 and 9.5.2), has served to explain the ways and the conditions under which PGx is currently used.

The study, through its two case studies, has highlighted the inability of any one methodological approach to cope with the present and future evolution of PGx. Instead it has been necessary to make choices from different theoretical traditions, ranging from sociology (studies on socio-technical systems), innovation (diffusion of innovations theory and user-producer interactions), technology forecasting (substitution theory) and a general background imputed from concepts drawn from systems thinking.

As we saw in Chapter 4, studies in health care organisations often focus on a single unit of analysis. This thesis, however, adopts a systemic perspective, looking at an array of different heterogeneous factors involved in drug development and service delivery; at their interactions and how these will influence PGx testing policies. This was illustrated in chapter four (see figure 4.1).

This investigation has been conducted at many different levels ranging from high level policy making to how matters are treated at 'street level', since the situation for PGx is seen to be made up of very detailed matters and procedures, exemplified by the handling of samples correctly, the testing procedures and informed consent, to far wider notions that influence policy making, where policy makers expertise in issues relating to PGx heavily influence the viability of the policies themselves. It is proposed that, although there are previous studies on TPMT testing, the depth and breadth of this one and the comparison

UK-Spain, has not been presented before. In regards to EGFR testing, no similar study has been done to the knowledge of the author.

As we have explained as the research has evolved, controversy and uncertainty are intrinsic to the process of diffusion of medical innovations, dominated by feedback mechanisms between the producers of the technology, the regulators and its final users. These user-producer relations imply that innovation undergoes a process of re-shaping and adaptation that requires mechanisms of "negotiation" between the different actors implicated in innovation development and delivery. For PGx, these mechanisms include: drug approval processes, post-marketing surveillance mechanisms, clinical guidelines and/or reimbursement policies. These are often controversial and become a bottleneck for the adoption of PGx in the clinic.

Studying the existing controversies and future uncertainties around TPMT and EGFR testing has served to uncover existing gaps in knowledge which may, in the future, make a contribution to informing policy on how PGx service delivery may be improved through a public health system such as the NHS. This way of proceeding has led to an understanding of the many elements in the situation now, and some possible ones for the future, together with their interdependencies, uncertainties and controversies via feedback mechanisms, describable under the STEEPV acronym. In itself this is believed to be unique. It should be noted here that future policy decisions on PGx will need to integrate all the elements arising from the research, using the STEEPV acronym for guidance, since all of them are inter-dependent.

Generalisations from the specifics of the two case studies, toward influences on the evolution of PGx, are difficult but have not been ignored. The table provided in the annex, together with the points enumerated in section 9.6 – Tackling Controversies and Uncertainties: Some Policy Recommendations provides some insights into the mechanisms that may contribute to overcoming the existing barriers for PGx adoption in a public health care system such as the NHS. The implementation of these mechanisms would require changes at a policy level, informed by some of the identified gaps in knowledge that currently hamper the translation of PGx into the clinic.

REFERENCES

ALLISON, M. (2008) Is personalised medicine finally arriving? *Nature Biotechnology,* 26**,** 509-17.

ALMARSDÓTTIR, A. B., BJÖRNSDÓTTIR, I. & TRAULSEN, J. M. (2005) A lay prescription for tailor-made drugs. Focus group reflections on pharmacogenomics. *Health Policy***,** 233-241.

ANDERSON, W., FITZGERALD, AND MANASCO, (1999) Current and Future Applications of Pharmacogenomics. New Horizons: . *Science and Practice Acute Medicine,* 7**,** 262-269.

ANSTEY, A. V., WAKELIN, S. & REYNOLDS, N. J. (2004) Guidelines for prescribing azathioprine in dermatology. *British Journal of Dermatology,* 151**,** 1123-1132.

ARENAS, M., MARINAKI, A., ANSARI, A. & SANDERSON, J. (2006) Typing TPMT and ITPase to detect azathioprine toxicity. *Personalised Medicine,* 3**,** 45-59.

ARENAS, M., SIMPSON, G., LEWIS, C. M., SHOBOWALE-BAKRE, E.-M., ESCUREDO, E., FAIRBANKS, L. D., DULEY, J. A., ANSARI, A., SANDERSON, J. D. & MARINAKI, A. M. (2005) Genetic Variation in the MTHFR Gene Influences Thiopurine Methyltransferase Activity. *Clin Chem,* 51**,** 2371-2374.

ARNOLD, H. P. & HALL, S. T. (2005) Pharmacogenomics and Clinical R&D. *Pharmacogenomics,* 6**,** 801-806.

ASTRAZENECA (2004) IRESSA Survival Evaluation in Lung cancer ISEL Trial Shows No Overall Survival Advantage in a Highly Refractory Population. *AstraZeneca News.*

ASTRAZENECA (2005a) IRESSA Label Change Press Release. *Iressa News.* Wilmington, DE.

ASTRAZENECA (2005b) IRESSA® (ZD1839, gefitinib) Tablets. Oncologic Drugs Advisory Committee (ODAC) Meeting Briefing Document.

ATTAR, M. & LEE, V. H. (2003) Pharmacogenomic considerations in drug delivery. *Pharmacogenomics,* 4**,** 443-461.

ATTRIDGE, J. (2006) Equity of Access to Innovative Medicines: Mission Impossible? *Pharmaceuticals and Government Policy,* 26**,** 17-23.

BIJKER, W. E. (1987) The Social Construction of Bakelite: Toward a Theory of Invention. IN BIJKER, W. E., HUGHES, T. P. & PINCH, T. (Eds.) *The Social Construction of Technological Systems.*

BIJKER, W. E. (1995) *Of Bicycles, Bakelites and Bulbs,* Cambridge - Massachusetts The MIT Press.

BIJKER, W. E. & LAW, J. (1992) *Shaping Technology. Building Society,* Cambridge (Massachussetts). London (England), The MIT Press.

BIRMINGHAM CITY HOSPITAL (2009) Thiopurine S-methyl transferase (TPMT) Service.

BLACKHALL, F., RANSON, M. & THATCHER, N. (2006) Where next for gefitinib in patients with lung cancer? *The Lancet Oncology,* 7**,** 499-507.

BRITISH THORACIC SOCIETY (2007) Single Technology Appraisal (STA). Erlotinib for the treatment of non small-cell lung cancer. Appeal. IN EXCELLENCE, N. I. F. H. A. C. (Ed.

BROWN, N., RAPPERT, B. & WEBSTER, A. (2000) Introducing Contested Futures: From Looking into the Future to Looking at the Future. IN BROWN, N., RAPPERT, B. & WEBSTER, A. (Eds.) *Contested Futures. A Sociology of Prospective TechnoScience.* Ashgate.

BUCHANAN, A., CALIFANO, A., KAHN, J., ROBERTSON, J., MCPHERSON, E. & BRODY, B. (2002) Pharmacogenetics: Ethical Issues and Policy Options. *Kennedy Institute of Ethics Journal,* 12**,** 1-15.

BUKAVECKAS, B. L. (2007) Pharma, clinicians and the lab come together over personalised medicine. *Personalised Medicine,* 4**,** 105-108.

CALLON, M. (1986a) The Sociology of an Actor-Network: The Case of the Electric Vehicle. IN MICHEL CALLON, J. L. A. A. R. (Ed.) *Mapping the Dynamics of Science and Technology.* The Macmillan Press Ltd.

CALLON, M. (1986b) Some elements of a sociology of translation: domestication of the scallops and the fishermen of St Brieuc Bay. IN LAW, J. (Ed.) *Power, Action and Belief. A New Sociology of Knowledge?* London, Boston & Henley, Routledge & Kegan Paul.

CALLON, M. (1987) Society in the Making: The Study of Technology as a Tool for Sociological Analysis. IN BIJKER, W. E., HUGHES, T. P. & PINCH, T. (Eds.) *The Social Construction of Technological Systems. New Directions in the Sociology and History of Technology.* The MIT Press.

CANCER RESEARCH UK (2008) Non-Small Cell Lung Cancer. *http://www.cancerhelp.org.uk.*

CARLSSON, B. & STANKIEWICZ, R. (1991) On the nature, function and composition of technological systems. *Journal of Evolutionary Economics,* 1**,** 93-118.

CARTER, M. J., LOBO, A. J. & TRAVIS, S. P. L. (2004) Guidelines for the management of inflammatory bowel disease in adults. On behalf of the IBD Section of the British Society of Gastroenterology. *International Journal of Gastroenterology and Hepatology,* 53**,** v1-v6.

COLEMAN, J. S., KATZ, E. & MENZEL, H. (1966) *Medical innovation : a diffusion study,* Indianapolis, Bobbs-Merrill.

COLLINS, F. S., GREEN E. D., GUTTMACHER A. E., GUYER M. S., (2003) A vision for the future of genomics research. *Nature,* 422**,** 835-847.

COLLINS, F. S. & MCKUSICK, V. A. (2001) Implications of the Human Genome Project for Medical Science. *Journal of American Medical Association,* 25.

COMIS, R. L. (2005) The Current Situation: Erlotinib (Tarceva®) and Gefitinib (Iressa®) in Non-Small Cell Lung Cancer. *The Oncologist,* 10**,** 467-470.

COMPAGNI, A., BARTOLI, S., BUEHRLEN, B., FATTORE, G., IBARRETA, D. & MESA, E. G. D. (2008) Avoiding adverse drug reactions by pharmacogenetic testing: A systematic review of the economic evidence in the case of TPMT and AZA-induced side effects. *International Journal of Technology Assessment in Healthcare,* 24**,** 294-302.

COOKE, P., HEINDENREICH, M., BRACZYK, H.J., (2001) *Regional Innovation Systems: The Role of Governances in a Globalised World*, Routledge.

COOMBS, R., GREEN, K., RICHARDS, A. & WALSH, V. (Eds.) (2001) *Technology and the Market: Demand, and Innovation,* Cheltenham, UK, Edward Elgar.

COULTHARD, S. & HOGARTH, L. (2005) The thiopurines: An Update. *Investigational New Drugs,* 23**,** 523-532.

CRUICKSHANK, J. (2003) *Critical Realism. The difference it makes,* London, Routledge.

CUNNINGHAM, P., GRANT-PEARCE, C., GREEN, L., MILES, I., RIGBY, J. & UYARRA, E. (2005) In sickness, in health and in innovation: NHS DIRECT - a health sector innovation study. *Administration,* 53**,** 42-65.

DALTON, W. S. & FRIEND, S. H. (2006) Cancer Biomarkers - An Invitation to the Table. *Science,* 312**,** 1165-1168.

DANZON, P. & TOWSE, A. (2002) The economics of gene therapy and of pharmacogenetics. *Value Health,* 5**,** 5-13.

DE MARINIS, F. & GROSSI, F. (2008) Clinical Evidence for Second- and Third-Line Treatment Options in Advanced Non-Small Cell Lung Cancer. *Oncologist,* 13**,** 14-20.

DENSCOMBE, M. (2007) The Good Research Guide for small-scale social research projects. Third Edition. Open University Press - McGraw-Hill.

DI MASI, J. (2002) The value of improving the productivity of the drug development process: faster times and better decisions. *Pharmacoeconomics,* 20**,** 1-10.

DI MASI, J., HANSEN, R. W. & GRABOWSKI, H. G. (2003a) The price of innovation: new estimates of drug development costs. *Journal of health Economics,* 22**,** 151-185.

DI MASI, J. A., HANSEN, R. W. & GRABOWSKI, H. G. (2003b) The price of innovation: new estimates of drug development costs. *Journal of Health Economics,* 22**,** 151-185.

DOH (2003) Government White Paper "Our inheritance, our future: realising the potential of genetics in the NHS". Department of Health.

DOSI, G. (1982) Technological Paradigms and technological trajectories. *Research Policy,* 11**,** 147-162.

DOSI, G. (1992) Research on Innovation Diffusion in Economics of Innovation - The Case of the Pharmaceutical Industry. *Rivista Internazionales di Scienze Sociali,* 3**,** 1-15.

DUBINSKY M C, REYES E, OFMAN J, CHIOU C F, WADE S & J., S. W. (2005) A cost-effectiveness analysis of alternative disease management strategies in patients with Crohn's disease treated with azathioprine or 6-mercaptopurine. American Journal of Gastroenterology. *American Journal of Gastroenterology,* 100**,** 2239-2247.

EC (1998) Directive 98-79-EC of the European Parliament and of the Council of 27 October 1998 on in vitro diagnostic medical devices. IN COMMISSION, E. (Ed. *L331/1.* Official Journal of the European Communities 7.12.98.

EC (2004) IVD GUIDANCE : Research Use Only products. A guide for manufacturers and notified bodies. European Commission. Entreprise Directorate General.

EMEA (2009) About EMEA - Structure. http://www.emea.europa.eu.

ESPICOM BUSINESS INTELLIGENCE LTD (2007) Cancer Drug Discoveries: What the Future Holds: Non-Small Cell Lung Cancer Chapter.

ETTINGER, D. S. (2006) Clinical Implications of EGFR Expression in the Development and Progression of Solid Tumours: Focus on Non-Small Cell Lung Cancer. *The Oncologist,* 11**,** 358-373.

EUROPEAN COURT OF HUMAN RIGHTS (1985) European Convention for Protection of Human Rights and Fundamental Freedoms. IN COUNCIL OF EUROPE (Ed. *European Treaties No. 5.*

EUROPEAN DIAGNOSTIC MANUFACTURERS ASSOCIATION (2008) IVDs in Europe. EDMA presents the 2007 Market Estimates.

EUROPEAN PATENT OFFICE (1973) Article 52: Patentable Inventions. European Patent Convention.

EUROPEAN PATENT OFFICE (2007) European Patent Convention. 13th Edition.

EVANS, W. & JOHNSON, J. (2001) Pharmacogenomics: the inherited basis for interindividual differences in drug response. *Annual Review of Genomics and Human Genetics,* 2**,** 9-39.

EVANS, W. E., HON, Y. Y., BOMGAARS, L., COUTRE, S., HOLDSWORTH, M., JANCO, R., KALWINSKY, D., KELLER, F., KHATIB, Z., MARGOLIN, J., MURRAY, J., QUINN, J., RAVINDRANATH, Y., RITCHEY, K., ROBERTS, W., ROGERS, Z. R., SCHIFF, D., STEUBER, C., TUCCI, F., KORNEGAY, N., KRYNETSKI, E. Y. & RELLING, M. V. (2001a) Preponderance of Thiopurine S-Methyltransferase Deficiency and Heterozygosity Among Patients Intolerant to Mercaptopurine or Azathioprine. *J Clin Oncol,* 19**,** 2293-2301.

EVANS, W. E. & RELLING, M. V. (1999) Pharmacogenomics: Translating Functional Genomics into Rational Therapeutics. *Science,* 286**,** 487-491.

EVANS, W. E., YI, Y., BOMGAARS, L., COUTRE, S. & HOLDSWOTH, M. (2001b) Preponderance of Thiopurine S-Methyltransferase Deficiency and Heterozygosity Among Patients Intolerant to Mercaptopurine or Azathioprine. *Journal of Clinical Oncology,* 19**,** 2293-2301.

EVIDENCE BASED MEDICINE WORKING GROUP (1992) Evidence-Based Medicine. A New Approach to Teaching the Practice of Medicine. *JAMA,* 268.

FARGHER, E., TRICKER K, NEWMAN B, ELLIOTT RA, ROBERTS S, SHAFFER J, BRUCE I & K., P. (2007) Current use of pharmacogenetic testing: a national survey of thiopurine methyltransferase testing prior to azathioprine prescription. *Journal of Clinical Pharmacy and Therapeutics,* 32**,** 187-95.

FDA (2004a) FDA Statement on Iressa. IN US FOOD AND DRUG ADMINISTRATION (Ed. *December 17, 2004.*

FDA (2004b) Innovation and Stagnation. Challenge and Opportunity on the Critical Path to New Medical Products.

FDA (2005) Guidance for Industry. Pharmacogenomic Data Submissions.

FLORDELLIS, C. S. (2005) The emergence of a new paradigm of pharmacogenetics. *Pharmacogenomics,* 6**,** 515-526.

FORD, L., GRAHAM, V. & BERG, J. (2004a) Individualising therapy; a new whole blood phenotypic assay for TPMT and concordance with genotyping. Sandwell and West Birmingham Hospitals NHS Trust.

FORD, L., GRAHAM, V. & BERG, J. (2004b) Patients with high TPMT activity identified during routine phenotypic testing-what is going on? **,** Sandwell and West Birmingham Hospitals NHS Trust.

FREEMAN, C. (1986) *The Economics of Industrial Innovation,* Cambridge, MA, The MIT Press.

GAISSER, S., HOPKINS, M. M., LIDDELL, K., ZIKA, E. & IBARRETA, D. (2009) The phantom menace of gene patents. *Nature,* 458**,** 407-408.

GARATTINI, S. & BERTELE, V. (2004) The role of the EMEA in regulating pharmaceutical products. IN MOSSIALOS, E., MRAZEK, M. & WALLEY, T. (Eds.). Open University Press.

GARDINER, S. J. & BEGG, E. J. (2006) Pharmacogenetics, Drug Metabolising Enzymes and Clinical Practice. *Pharmacological Review,* 58**,** 521-590.

GEELS, F. & RAVEN, R. (2006) Non-linearity and Expectations in Niche-Development Trajectories: Ups and Downs in Dutch Biogas Development (1973â€"2003). *Technology Analysis & Strategic Management,* 18**,** 375 - 392.

GEELS, F. W. (2008) The dynamics of sustainable innovation journeys. *Technology Analysis & Strategic Management,* 20**,** 521-536.

GELIJNS, A. & ROSENBERG, N. (1994) The dynamics of technological change in medicine. *Health Affairs,* 13**,** 28-46.

GELIJNS, A. C., ZIVIN, J. G. & NELSON, R. R. (2001) Uncertainty and Technological Change in Medicine. *Journal of Health Politics,* 26**,** 913-924.

GENENTECH (2007) Tarceva Fact Sheet.

GENZYME (2006) Genzyme launches diagnostic to monitor Gleevec resistance. *Pharmacogenomics.* Future Medicine.

GIBBONS, M., LIMOGES, C., NOWOTNY, H., SCHWARTZMAN, S., SCOTT, P. & TROW, M. (1994) *The New Production of Knowledge: the Dynamics of Science and Research in Contemporary Societies*, Sage Publications.

GISBERT, J., GOMOLLÓN, F., CARA, C., LUNA, M., GONZÁLEZ'LAMA, Y., PAJARES, J., MATÉ, J. & GUIJARRO, L. (2007a) Thiopurine Methyltransferase Activity in Spain: A Study of 14,545 Patients. *Digestive Diseases and Sciences,* 52**,** 1262-1269(8).

GISBERT, J., GOMOLLÓN, F., CARA, C., LUNA, M., LAMA, Y. G., PAJARES, J., MATÉ, J. & GUIJARRO, L. (2007b) Thiopurine Methyltransferase Activity in Spain: A Study of 14,545 Patients. *Digestive Diseases and Sciences,* 52**,** 1262-1269(8).

GISBERT, J. P., GONZÁLEZ-LAMA, Y. & MATÉ, J. (2006) Monitorización de la tiopurina metiltransferasa y de los metabolitos tiopurínicos para optimizar el tratamiento con azatioprina en la enfermedad inflamatoria gastrointestinal. *Gastroenterología y Hepatología,* 29**,** 568-83.

GLAXOSMITHKLINE (2002) Purinethol Prescribing Information.

GOLDSTEIN, D. B. (2003) Pharmacogenetics in the Laboratory and the Clinic. *New England Journal of Medicine,* 6**,** 553-556.

GRAHAM, V., FORD, L. & BERG, J. (2004) Twelve Months of Referral Service. Has it made a difference? **,** Sandwell and West Birmingham Hospitals NHS Trust.

GREEN, D. G. (1998) Why the NHS should retire at 50. *Institute of Economic Affairs.*

GREENHALGH, T. (2001) *How to Read a Paper. The basics of evidence based medicine,* London, BMJ Books.

GREENHALGH, T., ROBERT, G., MACFARLANE, F., BATE, P. & KYRIAKIDOU, O. (2004) Diffusion of Innovations in Service Organizations: Systematic Review and Recommendations. *The Milbank Quarterly,* 82**,** 581-629.

GREENHALGH, T., ROBERT, G., BATE, P., MACFARLANE, F. AND KYRIAKIDOU, O., (2005) *Diffusion of Innovations in Health Service Organisations*, BMJ Books.

GURWITZ, D., RODRIGUEZ-ANTONA, C., PAYNE, K., NEWMAN, W., GISBERT, J. P., MESA, E. G. D. & IBARRETA, D. (2009) Improving pharmacovigilance in Europe: TPMT genotyping and phenotyping in the UK and Spain. *European Journal of Human Genetics,* 17.

HABL, C., ANTONY, K. & ARTS, D. (2006) Surveying, Assessing and Analysing the Pharmaceutical Sector in the 25 EU Member States. Osterreichisches Bundesinstitut fur Gesundheitswesen. European Commission. DG Competition.

HAM, C. (2004) *Health Policy in Britain*, Palgrave Macmillan.

HANSEN, H. H. (2006) Non Small Cell Lung Cancer. An Update. *European Oncological Disease.*

HEDGECOE, A. (2004) *The Politics of Personalised Medicine*, Cambridge University Press.

HEDGECOE, A. (2006) Context, Ethics and pharmacogenetics. *Studies in History and Philosophy of Biological and Biomedical Sciences,* 37**,** 566-582.

HEDGECOE, A. & MARTIN, P. (2003) The Drugs Don't Work: Expectations and the Shaping of Pharmacogenetics. *Social Studies of Science,* 33**,** 327-364.

HENDERSON, R., ORSENIGO, L. & PISANO, G. P. (1999) The Pharmaceutical Industry and the Revolution in Molecular Biology: Interactions among Scientific, Institutional , and Organizational Change. IN MOWERY, D. C. & NELSON, R. R. (Eds.) *Sources of Industrial Leadership. Studies of Seven Industries.* Cambridge, Cambridge University Press.

HENEGHAN, C. & BADENOCH, D. (2002) *Evidevce-based Medicine Toolkit* Blackwell Publishing.

HERBST, R. S. & KIES, M. S. (2002) ZD1839 (Iressa^{TM}) in Non-Small Cell Lung Cancer. *The Oncologist,* 7**,** 9-15.

HIDEHARU, K. K., KASAHARA; MAKOTO, KAWAISHI; HIDEO, KUNITOH; TOMOHIDE, TAMURA; BRIAN, HOLLOWAY; AND KAZUTO, NISHIO; (2006) Detection of Epidermal Growth Factor Receptor Mutations in Serum as a Predictor of the Response to Gefitinib in Patients with Non Small-Cell Lung Cancer. *Clinical Cancer Research,* 12**,** 3915-3921.

HM GOVERNMENT & ASSOCIATION OF BRITISH INSURERS (2005) Concordat and Moratorium on Genetics and Insurance. IN HEALTH, D. O. (Ed.

HOGARTH, S. & MELZER, D. (2007) The IVD Directive and Genetic Testing: Problems and proposals. *20th meeting of Competent Authorities.* Lisbon.

HOLME, S. A., DULEY, J. A., SANDERSON, J., ROUTLEDGE, P. A. & ANSTEY, A. V. (2002) Erythrocytre thiopurine methyl transferase assessment prior to azathioprine use in the UL. *Q J Med,* 95**,** 439-444.

HOPKINS, M., ENZING, C. & HOGARTH, S. (2008) Intellectual Property Rights and Diagnostics: the Implications for Pharmacogenomics. Fraunhofer Institute for Systems and Innovation Research.

HOPKINS, M. H., LEWIS, G., GAISSER, S., RYAN, J., ENZING, C., HARTIG, L., VULLINGS, W. & FORDE, T. (2006) Regulatory and Quality Assurance Frameworks for Pharmacogenetics: A Comparative Study of the US, EU and Four Member States. Institute for Prospective Technological Studies.

HOPKINS, M. M. (2004) Technique-Led Technological Change and The 'Hidden Research System': Genetic Testing in the NHS. University of Sussex.

HUDSON, K. & JAVITT, G. (2009) Regulating laboratory-developed tests. *Nat Biotech,* 27**,** 419-420.

HUGHES, T. P. (1986) The Seamless Web: Technology, Science, Etcetera, Etcetera. *Social Studies of Science,* 16**,** 281-92.

HUGHES, T. P. (1987) The Evolution of Large Technological Systems. IN BIJKER, W., HUGHES, T. P. & PINCH, T. (Eds.) *The Social Construction of Technological Systems: New Directions in the Sociology and History of Technology.* The MIT Press.

HUGHES, T. P. (1989) The Evolution of Large Technological Systems. IN BIJKER, W., HUGHES, T. P. & PINCH, T. (Eds.) *The Social Construction of Technological Systems: New Directions in the Sociology and History of Technology.* The MIT Press.

HUMAN GENETICS COMMISSION (2002) Information-Gathering Session on Pharmacogenetics

IDIBAPS (2006) IBD Chip. LifeSciHealth Priority of the European Commission Sixth Framework Programme. European Commission. http://www.ibdchipproject.eu/.

INGELMAN-SUNDBERG, M. (2004) Pharmacogenetics of cytochrome P450 and its applications in drug therapy: the past, present and future. *Trends in Pharmacological Sciences,* 25.

ISPOR (2009) ISPOR Global Health Systems Road Map. International Society for Pharmacoeconomics and Outcomes Research.

JOLIVET, E., LARÉDO, P. & SHOVE, E. (2003) Managing Breakthrough Innovations: the SOCROBUST methodology. University of Lancaster, Universidad Carlos III, Universit de Toulouse I, University of Twente, ECN, CNR, Armines.

KALOW, W. (2002) Pharmacogenetics and Personalised Medicine. *Fundamental & Clinical Pharmacology,* 16**,** 337-342.

KATZ, D. A., HOVE, L. M. V. & SPEAR, B. (2002) Pharmacogenetics: an opportunity for codevelopment of pharmaceuticals and diagnostics. *Expert Review of Molecular Diagnostics,* 2**,** 291-294.

KLEIN, R. (2001) *The New Politics of the NHS,* Edinburgh, Pearson Education Limited. Prentice Hall.

LATOUR, B. (1986) The powers of association. IN LAW, J. (Ed.) *Power, Action and Belief. A New Sociology of Knowledge?* London, Boston and Henley, Routledge & Kegan Paul.

LAW, J. (1986) On the methods of long-distance control: vessels, navigation and the Portuguese route to India. IN LAW, J. (Ed.) *Power, Action and Belief. A New Sociology of Knowledge?* London, Boston & Henley, Routledge & Kegan Paul.

LEE, S. M. (2006) Is EGFR expression important in non-small cell lung cancer? *Thorax. An International Journal of Respiratory Medicine,* 61**,** 98-99.

LENNARD, L. & MADDOCKS, J. L. (1983) Assay of 6-thiopurine nucleotide, a major metabolite of azathioprine, 6-mercaptopurine and 6-thioguanine, in human red cells. *Journal Pharmacy and Pharmacology,* 35**,** 15-18.

LEWIS, G. (2003) The Clinical and Commercial Development of Pharmacogenetics. Project Outline.

LINDPAINTNER, K. (2002) Pharmacogenetics and the future of medical practice. *British Journal of Clinical Pharmacology,* 54**,** 221-230.

LINDPAINTNER, K. (2003) The impact of pharmacogenetics and pharmacogenomics. *Journal of Commercial Biotechnology,* 10**,** 60-77.

LITTLE, S. (2005) DxS Ltd. *Personalised Medicine,* 2**,** 135-138.

LOON, J. A. V. & WEINSHILBOUM, R. (1987) Human Lymphocyte Thiopurine Methyltransferase Pharmacogenetics: Effect of Phenotype on 6-Mercaptopurine-Induced Inhibition of Mitogen Stimulation. *The Journal of Pharmacology and Experimental Therapeutics,* 242**,** 21-26.

LOVERIDGE, D. (2002) The STEEPV acronym and process - a clarification. *Ideas in Progress.* PREST Policy Research in Engineering Science and Technology. The University of Manchester.

LOVERIDGE, D. (2004) Experts and foresight: review and experience. *International Journal of Foresight and Innovation Policy,* 1**,** 33-69.

LOVERIDGE, D. (2008) *Foresight: The Art And Science of Anticipating The Future*, Routledge.

LUNDVALL, B. A. (1992) *National Systems of Innovation,* London, Pinter.

MALERBA, F. (2002) Sectoral Systems of Innovation and Production. *Research policy,* 31**,** 247-264.

MARLE, E. V. D. A., GURWITZ, D., DETMAR, S. B., ENZING, C. M., HOPKINS, M. M., MESA, E. G. D. & IBARRETA, D. (2006) Cost-effectiveness of pharmacogenomics in clinical practice: a case study of thiopurine methyltransferase genotyping in acute lymphoblastic leukemia in Europe. *Pharmacogenomics,* 7**,** 783-792.

MARSHALL, E. (2009) Drug Metabolite Prompt Legal Battle. *Science,* 325.

MARTIN, P. (2001) Great Expectations: the construction of markets, products and user needs during the early development of gene therapy in the USA. IN COOMBS, R., GREEN, K., RICHARDS, A. & WALSH, V. (Eds.) *Technology and the Market. Demand, users and innovation.* Edward Elgar.

MARTIN, P., LEWIS, G., SMART, A. & WEBSTER, A. (2006) False Positive? The clinical and commercial development of pharmacogenetics. The University of Nottingham, The University of York and Bath Spa University.

MARTIN, P. & MORRISON, M. (2006) Realising the Potential of Genomic Medicine. Institute for the study of Genetics, Biorisks and Society, University of Nottingham.

MATTHIJS, G. (2006) The European opposition against the BRCA gene patents. *Familial Cancer,* 5**,** 95-102.

MCLAUGHLIN, J. (2001) EBM and risk. Rhetorical resources in the articulation of professional identity. *Journal of Management in Medicine,* 15**,** 352-363.

MCNEILL, P. & CHAPMAN, S. (1985) *Research Methods,* London and New York, Routledge.

MEDICAL RESEARCH COUNCIL (2003) UK ALL 2003 Protocol. UK National Randomised Trial for Children and Young Adults with Acute Lymphoblastic Leukaemia (ALL).

MELZER, D. (2003) My Very Own Medicine: What Must I Know?. Information Policy for Pharmacogenetics., The Wellcome Trust.

METCALFE, J. S., JAMES, A. & MINA, A. (2005) Emergent Innovation Systems and the Delivery of Clinical Services: The case of intra-ocular lenses. *Research Policy,* 34**,** 1283-1384.

MEYER, J. M. & GINSBURG, G. S. (2002) The path to personalised medicine. *Current Opinion in Chemical Biology,* 6**,** 434-438.

MHRA (2006) Sale and Supply of In Vitro diagnostic Medical Devices (IVDs)

MHRA (2009a) Detailed Drug Analysis Print interpretation guide. http://www.mhra.gov.uk.

MHRA (2009b) Licensing of Medicines. http://www.mhra.gov.uk.

MHRA (2009c) What is the Yellow Card Scheme? , http://yellowcard.mhra.gov.uk/.

MILBURN, A. (2001) Speech by Secretary of State for Health (Alan Milburn) at the Institute of Human Genetics, International Centre for Life, Newcastle upon Tyne, 19th April 2001. British Society for Human Genetics Office.

MILES, I. (2005) Innovation in Services. IN FAGERBERG, J., MOWERY, D. C. & NELSON, R. (Eds.) *The Oxford Handbook of Innovation.* Oxford University Press.

MILNE, C.-P. (2002) Orphan products—pain relief for clinical development headaches. *Nature Biotechnology,* 20**,** 780-784.

MORAN, M. (1999) *Governing the Healthcare State. A comparative study of the United Kingdom, the United States and Germany,* Manchester & New York, Manchester University Press.

MRC (2007) UKALL 2003. UK National Randomised Trial for Children and Young Adults with Acute Lymphoblastic Leukaemia (ALL). IN COUNCIL, M. R. (Ed., www.ctsu.ox.ac.uk via 'projects' then 'UKALL 2003'.

NATIONAL HORIZON SCANNING CENTRE (2009) NHSC National Horizon Scanning Centre.

NEED, A., MOTULSKY, A. G. & GOLDSTEIN, D. B. (2005) Priorities and standards in pharmacogenetic research. *Nature Genetics,* 37**,** 671-681.

NHS EXECUTIVE (6 August 1999) Health Service Circular 1999/176. National Institute for Clinical Excellence: initial work programme.

NICE (2008a). http://www.nice.org.uk/.

NICE (2008b) Erlotinib for the treatment of non-small-cell lung cancer. Final Appraisal Determination. National Institute of Clinical Excellence.

NICE (2008c) Lung cancer (non-small-cell) - gefitinib: Draft scope for consultation. The National Institute of Clinical Excellence.

NICE (2009) Measuring effectiveness and cost effectiveness: the QALY. The National Institute of Clinical Excellence.

NICE (April 2008) Final appraisal determination. Erlotinib for the treatment of non-small-cell lung cancer. National Institute for Health and Clinical Excellence.

NICE (February 2007) Final Appraisal Determination Erlotinib for the treatment of non-small-cell lung cancer. National Institute of Health and Clinical Excellence

NIELSEN, L. F. & MØLDRUP, C. (2006) Lay perspective on pharmacogenomics: a literature review. *Personalised Medicine,* 3**,** 311-316.

NIGHTINGALE, P. & MARTIN, P. (2004) The Myth of the Biotech Revolution. *Trends in Biotechnology,* 22.

NORTON, R. M. (2001) Clinical pharmacogenomics - applications in pharmaceutical R&D. *DDT,* 6**,** 180-185.

NOWGEN (2005) TARGET - The TARGET study (Pharmacogenetics). http://www.nowgen.org.uk/.

NOWGEN (2009) TARGET - The TARGET study. http://www.nowgen.org.uk/stories/199-target.

NUFFIELD COUNCIL ON BIOETHICS (2003) Pharmacogenetics: Ethical Issues. London.

OECD (1997) National Innovation Systems. Paris, Organisation for Economic Co-operation and Development.

OECD (2006) Innovation in pharmaceutical biotechnology: comparing National Innovation Systems at the Sectoral level.

PAEZ, J. G., JÄNNE, P. A., LEE, J. C., TRACY, S., GREULICH, H., GABRIEL, S., HERMAN, P., KAYE, F. J., LINDEMAN, N., BOGGON, T. J., NAOKI, K., SASAKI, H., FUJII, Y., ECK, M. J., SELLERS, W. R., JOHNSON, B. E. & MEYERSON, M. (2004) EGFR Mutations in Lung Cancer: Correlations with Clinical Response to Gefitinib Therapy. *Science,* 304**,** 1497-1500.

PAYNE, K., NEWMAN, W., FARGUER, E., TRICKER, K., BRUCE, I. N. & OLLIER, W. E. R. (2007) TPMT Testing in rheumatology: any better than routine monitoring? *Rheumatology.*

PAYNE, K., NEWMAN, W. G., GURWITZ, D., IBARRETA, D. & PHILLIPS, K. A. (2009) TPMT Testing in azathioprine: a "cost-effective use of healthcare resources"? *Personalized Medicine,* 6**,** 103-13.

PIAZZOLI, A. & RECCHIA, G. (2004) Pharmacogenetics and pharmacogenomics: are they still promising? *Pharmacological Research,* 49**,** 357-61.

PIRMOHAMED, M. (2006) Warfarin - almost 60 years old and still causing problems. *British Journal of Clinical Pharmacology,* 62**,** 509-511.

PIRMOHAMED, M., JAMES, S., MEAKIN, S., GREEN, C., SCOTT, A. K., WALLEY, T. J., FARRAR, K., PARK, B. K. & BRECKENRIDGE, A. M. (2004) Adverse drug reactions as a cause of admission to hospital: prospective analysis of 18820 patients. *British Medical Journal,* 329**,** 15-19.

PIRMOHAMED, M. & LEWIS, G. (2004) The implications for pharmacogenetics and pharmacogenomics for drug development and health care. IN MOSSAILOS, E., MRAZEK, M., AND WALLEY, T. (Ed.) *Regulating pharmaceuticals in Europe: striving for efficiency, equity and quality.* European Observatory on Health Care Systems Series. Open University Press.

POWELL, W. W. & GRODAL, S. (2005) Networks of Innovators. IN FAGERBERG, J., MOWERY, D. C. & NELSON, R. R. (Eds.) *The Oxford handbook of Innovation.* Oxford University Press.

PROMETHEUS (2006) Getting the most of your thiopurine therapy. Prometheus Diagnostics.

RAMLOGAN R., T. G. A. M. S. (2006) Networks of Knowledge: The distributed nature of medical innovation. CRIC. University of Manchester.

RIP, A. (1986) Controversies as Informal Technology Assessment. *Knowledge: Creation, Diffusion, Utilisation,* 8.

RIP, A. & KEMP, R. (1998) Technological change. IN RAYNER, S. & MALONE, E. L. (Eds.) *Human Choice and Climate Change.* Battelle Press.

ROBERTSON, J. A., BRODY, B., BUCHANAN, A., KAHN, J., AND MCPHERSON, E., (2002) Project HOPE. *Health Affairs,* 21.

ROCHE (2007) Final Appraisal Determination on The Single Technology Appraisal (STA) of Erlotinib for the treatment of relapsed non-small cell lung cancer (NSCLC). NOTICE OF APPEAL BY ROCHE PRODUCTS LIMITED.

ROGERS, E. M. (1962) *Diffusion of Innovations,* New York, The Free Press.

ROSES, A. D. (2000) Pharmacogenetics and the practice of medicine. *Nature,* 405**,** 857-865.

ROY CASTLE LUNG CANCER FOUNDATION (2007) Understanding Lung Cancer. http://www.roycastle.org/.

ROY CASTLE LUNG CANCER FOUNDATION AND CANCERBACKUP (2007a) Appeal against Final Appraisal Determination Erlotinib for the treatment of non-small-cell lung cancer.

ROY CASTLE LUNG CANCER FOUNDATION AND CANCERBACKUP (2007b) Appeal against Final Appraisal Determination Erlotinib for the treatment of non-small-cell lung cancer. National Institute of Clinical Excellence.

ROYAL COLLEGE OF PHYSICIANS (2007) The Single Technology Appraisal (STA) of Erlotinib for the treatment of relapsed non-small cell lung cancer (NSCLC). Appeal on behalf of the Royal College of Physicians and Association of Cancer Physicians.

ROYAL SOCIETY (2005) Personalised Medicines: Hopes and Realities.

RYE, C. B. & KIMBERLY, J. R. (2007) The Adoption of Innovations by Provider Organizations in Health Care. *Med Care Res Rev,* 64**,** 235-278.

SACKETT, D. L., ROSENBERG, W. M. C., GRAY, J. A. M., HAYNES, R. B. & RICHARDSON, W. S. (1996) Evidence based medicine: what it is and what it isn't. *BMJ,* 312**,** 71-72.

SCIENCEDAILY (2008) Iressa Proves Just As Effective As Chemotherapy For Lung Cancer.

SERVICE, R. F. (2006) The Race for the $1000 Genome. *Science,* 311**,** 1544-46.

SHAH, J. (2003) Economic and regulatory considerations in pharmacogenomics for drug licensing and healthcare. *Nature Biotechnology,* 21.

SHAH, J. (2004) Criteria influencing the clinical uptake of pharmacogenomic strategies. *British Medical Journal,* 328.

SHAH, R. R. (2006) Can pharmacogenetics help rescue drugs withdrawn from the market? *Pharmacogenomics,* 7**,** 889-908.

SHEPHERD, F. A., PEREIRA, J. R., CIULEANU, T., TAN, E. H. & HIRSH, V. (2005) Erlotinib in Previously Treated Non–Small-Cell Lung Cancer. *The New England Journal of Medicine,* 353**,** 123-132.

SHIGEMATSU, H., LIN, L., TAKAHASHI, T., NOMURA, M., SUZUKI, M., WISTUBA, I. I., FONG, K. M., LEE, H., TOYOOKA, S., SHIMIZU, N., FUJISAWA, T., FENG, Z., ROTH, J. A., HERZ, J., MINNA, J. D. & GAZDAR, A. F. (2005) Clinical and Biological Features Associated With Epidermal Growth Factor Receptor Gene Mutations in Lung Cancer. *Journal of the National Cancer Institute,* 97.

SIPP, D. (2004) "Fast-track" drug approvals hit speed bumps in Japan. *Nature.*

SKYES, R. B. (2000) *New Medicines, the practice of medicine and public policy*, Nuffield Trust.

SMART, A. (2006) A multi-dimensional model of clinical utility. *Int J Qual Health Care,* 18**,** 377-382.

SMITH, A. & STIRLING, A. (2008) Socio-ecological resilience and socio-technical transitions: critical issues for sustainability governance. ESRC STEPS Centre.

SMITH, R. D., CORREA, C. & OH, C. (2009) Trade, TRIPS, and pharmaceuticals. *The Lancet,* 373**,** 684-91.

SPEAKE, G., HOLLOWAY, B. & COSTELLO, G. (2005) Recent developments related to the EGFR as a target for cancer chemotherapy. *Current Opinion in Pharmacology,* 5**,** 343-349.

STOCKING, B. (1985) *Initiative and Inertia - Case Studies in the NHS*, Nuffield Provincial Hospitals Trust.

STREETON, R., COOKE, M. & CAMPBELL, J. (2004) Researching the researchers: using a snowballing technique. *Research Nurse,* 12**,** 35-46.

UTTERBACK, J. M. (1994) Invasion of a Stable Business by Radical Innovation. *Mastering the Dynamics of Innovation.* Boston, Massachusetts, Harvard Business School Press.

VAN DE VEN, A. H., E. POLLEY, D., GARUD, R. & VENKATARAMAN, S. (1999) *The Innovation Journey,* New York, Oxford, Oxford University Press.

VAN LENTE, H. (1993) Promising Technology. The Dynamics of Expectations in Technological Developments. *Department of Philosophy of Science and Technology.* University of Twente. The Netherlands.

VAN LENTE, H. (2000) Futures of the Present: From performativity to prehension. IN BROWN, N., RAPPERT, B. & WEBSTER, A. (Eds.) *Contested Futures. A sociology of prospective techno-science.* Ashgate.

VAN LOON, J. & WEINSHILBOUM, R. (1982) Thiopurine methyltransferase biochemical genetics:Human lymphocyte activity. *Biochemical Genetics,* 20**,** 637-58.

VENTER, J. C., ADAMS, M. D., MYERS, E. W., LI, P. W., MURAL, R. J., SUTTON, G. G., SMITH, H. O., YANDELL, M. & EVANS, C. A. (2001) The Sequence of the Human Genome. *Science,* 291**,** 1304 -1351.

VON HIPPEL, E. (1988) *The Sources of Innovation,* New York, Oxford, Oxford University Press.

VON HIPPEL, E. (2005) *Democratizing Innovation*, The MIT Press.

WAKELING, A. E., GUY, S. P., WOODBURN, J. R., ASHTON, S. E., CURRY, B. J., BARKER, A. J. & GIBSON, K. H. (2002) ZD1839 (Iressa): An Orally Active Inhibitor of Epidermal Growth Factor Signaling with Potential for Cancer Therapy. *Cancer Research,* 62**,** 5749–5754.

WEBSTER, A., MARTIN, P., LEWIS, G. & SMART, A. (2004) Integrating pharmacogenetics into society: in search of a model. *Nature Reviews Genetics,* 5**,** 663-668.

WEINBERG, A. M. (1972) Science and trans-science. *Minerva,* 10**,** 209-22.

WEINSHILBOUM, R. (2001) Thiopurine Pharmacogenetics: Clinical and Molecular Studies of Thiopurine Methyltransferase. *Drug Metab Dispos,* 29**,** 601-605.

WEINSHILBOUM, R., RAYMOND, F. & PAZMIÑO, P. (1978) Human erythrocyte thiopurine methyltransferase: radiochemical microassay and biochemical properties. *Clinica Chimica Acta; International Journal of Clinical Chemistry,* 2**,** 323-33.

WEINSHILBOUM, R. M. & SLADEK, S. L. (1980) Mercaptopurine Pharmacogenetics: Monogenic Inheritance of Erythrocyte Thiopurine Methyltransferase Activity. *American Journal of Human Genetics,* 32.

WILLIAMSON, C. (2008) Alford's theoretical political framework and its application to interests in health care now. *British Journal of General Practice.*

WILSON, D. (2006) Acquisition and disclosure of genetic information under alternative policy regimes: an economic analysis. *Health Economics, Policy and Law,* 1**,** 263-276.

WINTER, J., WALKER, A., SHAPIRO, D., GAFFNEYS, D., SPOONER, R. J. & MILLS, R. P. (2004) Cost-effectiveness of thiopurine methyltransferase genotype screening in patients about to commence azathioprine therapy for treatment of inflammatory bowel disease. *Alimentary Pharmacology & Therapeutics,* 20**,** 593-99.

WOELDERINK, A., IBARRETA, D., HOPKINS, M. M. & EMILIO RODRÍGUEZ-CEREZO (2005) The current clinical practice of pharmacogenetic testing in Europe: TPMT and HER2 as case studies. *The Pharmacogenomics Journal (2005),* 1-5.

WOODSON, L. & WEINSHILBOUM, R. (1983) Human kidney thiopurine methyltransferase: purification and biochemical properties. *Biochemical Pharmacology,* 32**,** 819-826.

ZARTMAN, I. W. (2005) Comparative Case Studies. *International Negotiation,* 10**,** 3-16.

ZIKA, E., GURWITZ, D. & IBARRETA, D. (2006) Pharmacogenetics and pharmacogenomics: State-of-the-art and potential socio-economic impact in the EU. IPTS Institute for Prospective Technological Studies.

ANNEXES

Annex 1 – Ethical Approval

MANCHESTER 1824

The University of Manchester

Secretary to Dr. T Stibbs
Room 2.005
John Owens Building
The University of Manchester
Oxford Road
Manchester M13 9PL

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ref: TPCS/CA/ethics/07273

7th March 2008

Ms G Sainz De La Fuente,
Manchester Business School,
Harold Hankins Building, Room 7.09,
Oxford Road, University Precinct

Dear Ms Sainz De La Fuente,

Committee on the Ethics of Research on Human Beings

07273 Sainz De La Fuente,: Pharmacogenetic's Controversies and Healthcare Options: The Shaping of New Mechanisms of Service Delivery in the case of Thiopurine Methyltrasferase (TPMT) and Epidermal Growth Factor Receptor (EGFR) testing. (South West ref: 08/H0206/5)

I write to confirm that at its meeting on 6th March 2008, the Committee received the report on the above project, which had been approved by a recognised ethics committee. That approval is therefore endorsed by the University Ethics Committee.

If you have cause to inform the REC of any unusual or unexpected results that raise questions about the safety of the research, you should also forward a copy to our office. We also ask that you provide us with details of any substantial amendments approved by the REC.

I am pleased to say that we now have a facility to accept and store electronic versions of documents, particularly copies of COREC application forms. From now on, therefore, electronic documents can be emailed to me at the address below. We are happy to accept documents in hard copy. Typically LREC approval letters will be in this form and we would prefer to have the ethics insurance form as a hard copy with a signature.

Yours sincerely

Catherine Atkinson
Secretary to Dr T P C Stibbs
Catherine Atkinson
Compliance and Risk Management
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26 March 2009

Ms Graciela Sainz De La Fuente
Doctoral Researcher
Manchester Institute of Innovation Research (Manchester Business School)
Harold Hankins Building, Room 7.09
Oxford Road- University Precint
Manchester
M13 9PL

Dear Ms Sainz De La Fuente

Full title of study: **Pharmacogenetic's Controversies and Healthcare Options: The Shaping of New Mechanisms of Service Delivery in the case of Thiopurine Methyltransferase (TPMT) and Epidermal Growth Factor Receptor (EGFR) testing.**

REC reference number: **08/H0206/5**

Thank you for sending the declaration of end of study form, notifying the Research Ethics Committee that the above study concluded on 23 December 2008. I will arrange for the Committee to be notified.

A summary of the final research report should be provided to the Committee within 12 months of the conclusion of the study. This should report on whether the study achieved its objectives, summarise the main findings, and confirm arrangements for publication or dissemination of the research including any feedback to participants.

REC Reference: 08/H0206/5	**Please quote this number on all correspondence**

Yours sincerely

Geoffrey Stark
Assistant Administrator

Email: Southwest.REC@nhs.net

Copy to: Dr Karen Shaw, The University of Manchester

Annex 2 - Letter of participation in Study

The University of Manchester

Manchester, <Day> <Month> 2008

Dear <FULL NAME>,

My name is Graciela Sáinz and I am a PhD student at the Manchester Institute of Innovation Research (formerly PREST), which is part of the Manchester Business School at the University of Manchester. My studies are being supervised by Dr. Michael Keenan and Professor Denis Loveridge.

I have a background is molecular biology and I am now doing a PhD on Innovation Policy, focusing on the dynamics of innovation in pharmacogenetics. In particular I am looking at how the implementation of certain genetic tests might reshape the organisational structures that control service delivery. This research is being conducted through the use of two case studies Thiopurine Methyl Transferase (TPMT) testing in Acute Lymphoblastic Leukaemia and Epidermal Growth Factor Receptor (EGFR) in Non-Small Cell Lung Cancer.

I have known of you from my literature search, (BY PERSONAL RECOMMENDATION) and the seminars I have attended. Your work is very relevant for my research on pharmacogenetics and innovation policy, relating to its possible influence in the future of clinical practice. For this I am analysing how the future clinical application of pharmacogenetics might have consequences in health service delivery and in particular in innovation dynamics.

I would very much appreciate learning how you foresee the clinical implementation of pharmacogenetics and genetic testing since my research is future oriented research and I rely on the opinions of experts in the field.

The outcome of the research will represent possible futures for the application of pharmacogenetics in the clinic, based on the opinions of experts currently researching the evolution of the clinical science, the development of pharmacogenetic treatments and associated instruments by the pharmaceutical industry, and implementation by clinicians.

If you are willing to interviewed (SUBJECT), the interview itself will last about an hour. It will be in confidence and all the information will be used anonymously. Subsequently, I would give you some feedback, sending you further information on the progress of the research. I hope it may be possible to be able to organise a workshop where the contributing experts meet, in order to share and discuss how they foresee the future evolution of pharmacogenetics.

Thank you in anticipation.
Yours Sincerely,
Graciela Sáinz

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Annex 3 - Interview Guides

General Pharmacogenetics Questions

1. Is it generally accepted that PGx can be used to detect adverse drug reactions and/or improve the prescription? Are there other main applications PGx?

2. Genetic tests can either act as a diagnostic test or predict how a patient's disease will progress or act as a prognostic test. Are both cases accepted in the same way or is there any preference when it applies to the clinic?

3. To what extent are genetic tests are the critical point for personalised medicine and there are not other markers that are sufficiently consistent to guide treatment?

4. The application of PGx needs clinical validity, utility, prove of cost-effectiveness and clinical and public acceptance. Even in such situation the level of implementation is different?

5. Which group or institution puts the major burden for the non-implementation of PGx? Why?

6. When are the Medicines and Health Regulatory Agency and NICE expected to introduce specifications for using genetic information before prescribing? When they get enough information from clinical trials? When there is a demonstrated benefit for health?

7. Will new PGx services need an organisational reorientation of the health system? Which new infrastructures/new relationships and services will require?

8. How do you foresee pharmacogenetics to be implemented in the future?

9. Which strategies are being envisaged for the implementation of PGx services in the future?

TPMT-related questions addressed to pharmaceutical and biotechnology companies

- 1. Pharmaceutical companies are shifting in some cases from a 'blockbuster' to a minibuster's business model. Is there any interest in reintroducing thiopurine drugs into the market for a narrower condition (as orphan drugs)?
- 2. How do companies face clinical trials? Would there be any kind of retrospective look at previous trials and adapt specific genetic biomarkers to develop new drugs?. Would pharmaceutical companies carry out pharmacodiagnostic and clinical trials at the same time for the co-development drug – test?
- 3. Is there at the moment any new drug under development for similar treatments as thiopurine drugs?
- 4. Is it possible that thiopurine drugs get a product license for TPMT testing, as it occurred in the US with the labelling for mercaptopurine? Would there be any interest in co-developing thiopurine drugs-test?
- 5. Is it feasible that a private company markets a TPMT genotyping test (which needs approval), when TPMT phenotyping is carried in some hospital units (which do not need approval but just accreditation)?
- 6. One of the key strategies during the promotion of Herceptin was the provision of free HER2 test to clinicians in certain reference centres. In the case of TPMT, in Spain for example, Celltech UCB Pharma is providing free testing for Chron´s patients. Is there any company operating in the UK in the same terms?
- 7. Gene chips for P450 are very expensive; nevertheless, is it expected that TPMT could end in a similar type of device?
- 8. If not on a chip, would it be possible to create lab-on-a-chip for TPMT?

TPMT-related Questions addressed to Clinicians, Researchers and Patient Associations

1. What are the criteria for prescribing 6-mercaptopurine or 6-azathioprine in different specialities when there are no studies that reveal more benefit from one than another?
2. Why the guidelines for TPMT testing are different in different clinical associations?
3. Who makes the decision of TPMT testing? Is it the clinician, the pharmacogenetics laboratory or the geneticist?
4. Who interpret the test? Again, is it the clinician, the pharmacogenetics laboratory or the geneticist?
5. If TPMT is implemented in the future, how relations among clinicians, geneticists and pharmacogenetics labs are expected to evolve?
6. What is the engagement of patient associations in TPMT testing?
7. How do clinicians perceive currently the use of TPMT testing in clinical practice for detecting ADRs related to thiopurines?
8. If a drug (such as an orphan drug) was introduced into the market with a license for TPMT pre-testing. Would this change the concept of TPMT as preventing ADRs to TPMT as driving therapy? How would this influence the perception of practitioners regarding TPMT testing?
9. How is TPMT related information managed at the hospital? Who keeps it? For how long? For which future use can it be used? Is there any relation with the existing biobanks?
10. Despite what clinical guidelines recommend; is informed consent always applied?
11. In Spain, the monitoring of TPMT is carried out only in patients with inflammatory bowel disease because there is not enough "market" for other conditions. Can this be the same reason in the UK?
12. A European study reveals that TPMT testing for Acute Lymphoblastic Leukaemia is cost-effective, especially in children. Is this acknowledged in the UK? Has this have any influence for TPMT testing for this disease? How about other conditions?

1) In the UK there are two big ongoing clinical trials for TPMT testing. The first one, the TARGET study, funded by the Department of Health intends to assess the cost-effectiveness of TPMT testing against traditional methods in various diseases, not including leukaemia. The second study, funded by the Leukaemia Research Fund and the Medical Research Council intends to assess the benefits of TPMT in Leukaemia patients. Is leukaemia considered marginal for TPMT testing and is this why a patient group has to engage into a clinical trial?

   ▪

EGFR-related questions addressed to pharmaceutical and biotechnology companies

- 1. In the case of Herceptin and HER2 test, the test was seen as necessary because only 20-30% of the patients of breast cancer would have the mutation that would make them eligible to Herceptin. In the case of EGFR this situation is different. Almost 90% of Non Small Cell Lung Cancers patients are EGFR positive, which makes genetic testing in many cases unnecessary. Which arguments support EGFR testing?
- 2. Is there any pharmacodiagnostic trial for EGFR testing? How is the current legislation for clinical trials going to change in the case of pharmacodiagnostics so as to facilitate EGFR the prove of validity and efficacy of EGFR?
- 3. Are private companies promoting EGFR testing? Why and What for?
- 4. Which strategies are private companies adopting for promoting EGFR testing?
- 5. Which strategies is AstraZeneca developing to overcome the problem of the withdrawal of Gefitinib (Iressa)? Is it thinking on using EGFR testing?
- 6. Is DxS willing to engage with a big pharma for launching a pharmacodiagnostic clinical trial? Is AstraZeneca willing to associate with DxS to relaunch Iressa?
- 7. How is AstraZeneca dealing with competition coming from Roche, the developer of Erlotinib (Tarceva)? Are DxS and Roche engaged in any agreement for co-development of drug and test?
- 8. Have private companies established any kind of relation with patient associations in relation to EGFR for prescribing Iressa or Tarceva? How have they done so? Have

private companies established any kind of relation with any other clinical/research group?

- EGFR-related Questions addressed to Clinicians, Researchers and Patient Associations
- 9. In the case of Herceptin and HER2 test, the test was seen as necessary because only 20-30% of the patients of breast cancer would have the mutation that would make them eligible to Herceptin. In the case of EGFR this situation is different. Almost 90% of Non Small Cell Lung Cancers patients are EGFR positive, which makes genetic testing in many cases unnecessary. Which arguments support EGFR testing in this situation?
- 10. Is the discovery of EGFR perceived as a real solution or is it perceived just as another promise to add to traditional chemotherapy? What would EGFR need to be implemented?
- 11. How would the application of EGFR in the clinic change the way of providing treatment for non-small cell lung cancer?
- 12. What is the position of the Clinical Associations in relation to EGFR? Do they foresee to change their guidelines and use genetic testing? Would this only depend on NICE decision?
- 13. Do clinicians believe EGFR tests are a useful solution for lung cancer or are they reluctant to use them because lung cancer has an important behavioural component? Does this influence its implementation?
- 14. NICE has already considered EGFR testing is not worth it. Is there still any hope on EGFR testing despite NICE position? How NICE decision could change?
- 15. Mutations in EGFR are correlated with lung cancers and response to gefitinib, although some patients who do respond to the drug do not show such mutations. To what extent is this argument being used not to implement EGFR testing in the clinic?
- 16. If 90% of the cases on NSCLC are EGFR positive, and NICE is not interested in EGFR; would it be possible to use a test for EMP-1/integrin to detect non-responders to Gefitinib and Erlotinib? Could it be used in substitution of EGFR test?

- 17. How would clinicians perceive the search for non-responders instead of responders?
- 18. The Roy Castle Lung Cancer Foundation is the only patient association dedicated to lung cancer. It is currently carrying out epidemiological studies on lung cancer. To what extent these epidemiological studies take EGFR into account? Does it foresee the introduction of this testing in NSCLC patients?
- 19. What pressure can this association exert on the health system for the introduction of genetic testing?
- 20. Is the Roy Lung Castle Foundation engaged with private companies in the development of NSCLC treatments?

Annex 4 - Mini-questionnaire addressed to clinical oncologists

The University of Manchester
Manchester
Business School

MANCHESTER 1824

Pharmacogenetics to improve drug efficacy: The case of EGFR testing in the UK

Traditional therapies for non-small cell lung cancer are now challenged by a new set of oral drugs, the tyrosin-kinase inhibitors (Gefitinib-*Iressa*® and Erlotinib-*Tarceva*®). These drugs promise higher survival rates, not only in non-small cell lung cancer but also in other conditions. However, these therapies are not currently used as a first line treatment; *Iressa*® was never approved in Europe, and *Tarceva*® was approved in some cases only.

In the UK, the guidance that the National Institute of Clinical Evidence (NICE) gave, was to provide *Tarceva*® as second and third line treatment; decision which faced the opposition of Roche, the Roy Castle Lung Cancer Foundation, the Association of Cancer Geneticists and the Royal College of Physicians. However, the decisions taken by NICE are important as they fall into the reimbursement mechanisms provided by NHS, and these at the moment do not cover the use of *Tarceva*® as a first line treatment. Nevertheless, NICE, during the *Tarceva*® appraisal, suggested further sub-group analysis that showed survival improvements associated to the drug. One of the options of such sub-group analysis, was looking for associations between EGFR mutations/amplifications and drug response, which have been reported in the literature; although the validity of such associations has not yet been fully proved.

It is therefore uncertain what the impact of *Tarceva*® (and eventually also *Iressa*®) will be for the treatment of non-small cell lung cancer; as well as it is uncertain how EGFR biomarkers may contribute to further guidance on the use of *Tarceva*® in the UK. At present, the introduction of any genetic component that assess drug response, depends on a set of different factors: the results of clinical trials, institutional support, clinical demand, patient's acceptance, validity of current monitoring methods, new drugs on the market or costs of testing.

This PhD project intends then to analyse, what the impact of these factors in the context clinical practice is for the specific case of Tarceva®; identify the main arising controversies associated to the use of this drug, and illustrate future options for new mechanisms of service delivery in non-small cell lung cancer.

The following questionnaire intends to gather the experience, opinion and visions of clinicians working in the area, aiming to understand, under a clinical expert perspective, the feasibility of the introduction of *Tarceva*® (and eventually also *Iressa*®), into clinical practice.

This research has been approved by a National Research Ethics Committee and by the Christie's Hospital Trust, and consequently, all the information will be processed anonymously.

Your time filling this questionnaire is very much appreciated.

The case of EGFR testing in lung cancer therapies QUESTIONNAIRE

Please, copy and paste the sign √ on the following boxes	YES	NO	comments
1. Are you a clinical oncologist treating lung cancer?			
2. How many lung cancer patients do treat every year?			
3. How many of these patients do you treat with Tarceva®?			
4. Do you think Tarceva® has a considerable advantage in second/third line treatment over alternative therapies?			
5. Apart from NICE guidance, which other factors (clinical trials, peers opinions, decisions at a local level…) may, in the future, drive the widespread use of Tarceva® as second/third line therapy?			
6. At the moment NICE doesn't recommended Tarceva® as a first line treatment, but, in a future hypothetical situation you thought Tarceva® may have an advantage over alternative therapies in first line treatment (because of recent clinical trials, publications, peer's experience…), would you consider to prescribe it?			
7. Do you think Tarceva® has a considerable advantage over Iressa®?			
8. Do you think Docetaxel® has a considerable advantage over Iressa®?			
9. Have you been involved in the Iressa® Clinical trials (ISEL)?			
10. Have you been involved in the Tarceva® Clinical trials (TALENT & TRIBUTE)?			
11. Do you think EGFR testing will facilitate the widespread use of Tarceva® as second/third line treatment?			
12. Do you think, in the future, it may be possible that EGFR testing will facilitate the use of Tarceva® as first line treatment?			
13. Do you think EGFR testing may facilitate the introduction of Iressa® into the market?			
14. Would you be in favour of EGFR testing if it was reimbursed so that some patients could expect to benefit from Tarceva®?			
15. Would you be in favour of EGFR testing if it wasn't reimbursed?			

Annex 5 – Controversies, Uncertainties and Policy Recommendations

Existing UNCERTAINTIES and CONTROVERSIES that hamper the diffusion of PGx into clinical practice.		What is possible for PGx service delivery?	Due to the present situation, what is feasible for PGx service delivery?	Informing future policy options: what is desirable? How can PGx delivery in the NHS be improved?
TPMT Testing Uncertainties	TPMT enzyme tests *vs*. TPMT genetic tests	It is possible to develop enzyme tests to measure the levels of TPMT in the blood, as well as developing genetic tests for detecting the different known TPMT polymorphisms implicated in the response to AZA/6-MP (provided the molecular reagents to do such analysis are available).	At the moment it is feasible to do TPMT enzyme tests and TPMT genetic tests for the most frequent polymorphisms implicated in drug response. It is, however, not yet feasible to do genetic analysis for all the known TPMT polymorphisms (more than 20) in the NHS, in which, with the technology available at the moment, a more extensive genetic analysis would be a lengthy and costly process.	- Implement cost-effective PGx services, not only for TPMT testing but also for other molecular biomarkers. In order to do this, it might be necessary to exploit the technical capacity of the clinical laboratories within the NHS and develop in-house "home-brew" tests. - Define adequate standards of testing that set out which genetic polymorphisms have a clearly defined implication in drug response and should therefore be looked at. - Establish a legal framework through which these NHS PGx services are protected from private monopolies.
	Innovative genetic technologies and future TPMT services	Biochip technologies have enabled the inclusion of TPMT polymorphisms in the IBD Chip, a technology which analyses 100 mutations in different genes simultaneously and assesses individual response (diagnosis and prognosis) to drugs in the treatment of Inflammatory Bowel Disease. The IBD chip is the first biochip (for testing response to drugs in IBD) of these characteristics.	The use of the IBD chip might be an option for very particular conditions (for which a biochip is available - at the moment only for IBD). However, its high price compared to other PGx testing methods used in clinical laboratories, makes it too expensive to be reimbursed by the NHS as yet.	It might be advisable to: - Integrate genetics knowledge into technology development, in order to deliver fast, multi-gene diagnostics. - Receive public support for their implementation in the NHS, where needed.

Existing UNCERTAINTIES and CONTROVERSIES that hamper the diffusion of PGx into clinical practice.		What is possible for PGx service delivery?	Due to the present situation, what is feasible for PGx service delivery?	Informing future policy options: what is desirable? How can PGx delivery in the NHS be improved?
TPMT Testing Uncertainties	TPMT "Home-Brew" tests vs. TPMT In-Vitro-Diagnostics	At present, there are both "home-brew" and IVD tests for TPMT testing. However, the use of "home-brews" prevails in the UK while IVDs are mostly used in the US.	In the NHS setting, the high cost of commercial TPMT IVD tests makes it infeasible to use them in the NHS. In any case, in the UK, TPMT is offered through "home-brew" tests.	At the moment there is a lack of regulation over the use of "home-brew" tests in the NHS. It which might be necessary to establish a regulation that controls how "home-brew" services should be provided. This should also include aspects of patient confidentiality and sampling and storage of biological samples.
	Centralisation vs. De-centralisation of TPMT testing services	TPMT testing services could be either centralised or de-centralised depending on the technical (e.g. HPLC or Mass Spectrometers) and physical infrastructures (PGx laboratories) available in the NHS.	At present TPMT services are centralised in the UK in two reference laboratories, one in Guy's Hospital in London and the other in Birmingham City Hospital. These two laboratories cover the current UK demand that exists for TPMT testing services.	The centralisation or de-centralisation of PGx services should be assessed in the context of the clinical demand for PGx testing, in the context of studies on clinical utility and cost-effectiveness, as well as NICE statutory guidelines. With the increase in demand for PGx services, it might be necessary to create PGx laboratories, instead of PGx services within existing clinical or research laboratories.

Existing UNCERTAINTIES and CONTROVERSIES that hamper the diffusion of PGx into clinical practice.		What is possible for PGx service delivery?	Due to the present situation, what is feasible for PGx service delivery?	Informing future policy options: what is desirable? How can PGx delivery in the NHS be improved?
TPMT Testing Controversies	TPMT Enzyme Tests for Incrementing Drug Doses	At present, it is only possible to determine with accuracy if a patient is likely to develop a severe ADR and therefore should be withdrawn from treatment with AZA or 6-MP, or whether s/he should be given a lower dose of the drug. No clinical proof has demonstrated (only indicated in some cases) that TPMT levels could be associated with an increase in drug doses.	The lack of clinical evidence makes it infeasible to use, in a safe and efficacious way, TPMT testing to increase drug doses.	It is necessary to demonstrate the clinical utility and validity (through clinical trials) of establishing an association between high levels of TPMT and increased doses of AZA or 6-MP, which may also be extended to other drug-test associations.
	TPMT Testing, Clinical Utility and Good Clinical Practice	At the moment there is not enough data about the clinical utility of TPMT testing (phenotyping and genotyping) because clinical trials are still under way. Once clinical trial data is available, it could be taken up by NICE and by different professional associations, who set the rules and recommendations on the treatments that should be implemented in healthcare. However, it is not always possible to conclude that clinical utility leads, necessarily, to good clinical practice, because clinicians (as EBM states) make assessments on the basis of what the guidelines say, but also, based on their own clinical judgement.	At the moment, despite the lack of results from clinical trials, it is feasible to request a TPMT test within the NHS, provided the local Trust that requests the test is willing to pay for it.	Develop integrated mechanisms, where diagnostic testing is integrated with the current model of EBM and is therefore considered a parameter of good clinical practice.

Existing UNCERTAINTIES and CONTROVERSIES that hamper the diffusion of PGx into clinical practice.		What is possible for PGx service delivery?	Due to the present situation, what is feasible for PGx service delivery?	Informing future policy options: what is desirable? How can PGx delivery in the NHS be improved?
TPMT Testing Controversies	The cost of TPMT testing and the setting up of pre-screening policies	It is currently possible to establish TPMT testing pre-screening policies (as some NHS Trusts have done), even when the cost-effectiveness of TPMT testing is contested.	The feasibility of establishing pre-screening policies depends on to what extent TPMT testing is a priority for the NHS Trust in the context of other treatments, which also depends on how many patients are undergoing treatment with AZA or 6-MP.	It might be desirable that TPMT testing is reimbursed by the NHS so that NHS Trusts do not have to face the dilemma of whether or not to set up TPMT pre-screening policies.

Existing UNCERTAINTIES and CONTROVERSIES that hamper the diffusion of PGx into clinical practice.		What is possible for PGx service delivery?	Due to the present situation, what is feasible for PGx service delivery?	Informing future policy options: what is desirable? How can PGx delivery in the NHS be improved?
EGFR Testing Uncertainties	Type of EGFR biomarker used to predict response to Tarceva®	At the moment, despite the fact that there is some indication of the implications of some mutations on the EGFR gene for response to Iressa® and Tarceva®, it is not yet clear whether those mutations can be used as predictors of drug response in clinical practice, because there is not enough scientific evidence to support that claim. Nor is there enough scientific knowledge about the interaction between different mutations on the EGFR gene and drug response.	It is feasible to use EGFR mutation kits for research purposes, although due to the lack of clinical utility, it is not yet possible to use these tests in clinical practice in the NHS. Nevertheless, some of these tests are commercially available and can be used in a private healthcare setting, if a patient is willing to pay for it.	More research is needed to identify which mutations are good predictors of drug response. Research needs to be supported by clinical trials.
	EGFR used as a prognostic biomarker	It is not yet possible to use EGFR testing as a prognostic biomarker, to evaluate the progression of non-small-cell lung cancer.	It is not feasible to introduce EGFR testing as a prognostic biomarker. As the box above indicates, neither is it feasible to use it as a diagnostic biomarker.	Prove the clinical utility of biomarkers that can make prognostic associations between genetic mutations and the evolution of diseases.
	Re-introduction of Iressa® on the UK market	Iressa® is not approved in the UK but it is approved in Asian countries like Japan. It might be possible to re-introduce the drug onto the UK market, provided there was clinical evidence that a biomarker (phenotypic or genetic) could enable the selection of good respondents, who would benefit from Iressa®.	Unless such clinical information is obtained, it will not be feasible to use Iressa® in the NHS.	Design clinical trials that include molecular determinants of drug response such as EGFR mutations.

Existing UNCERTAINTIES and CONTROVERSIES that hamper the diffusion of PGx into clinical practice.		What is possible for PGx service delivery?	Due to the present situation, what is feasible for PGx service delivery?	Informing future policy options: what is desirable? How can PGx delivery in the NHS be improved?
EGFR Testing Controversies	Country Differences in the approval of Iressa® and Tarceva®	It was possible to introduce Iressa® in Japan because the country has a fast track system for drug approval and also because NSCLC patients of Asian origin have been shown to respond better to the drug.	It is not feasible to adopt the same regulatory procedures in Japan and in the UK, because regulations for pharmaceuticals apply at a local level.	It will be beneficial to use Iressa® in the UK, only if it is proven to improve the survival and quality of life of NSCLC patients.
	NICE appraisal of the use of Tarceva®	According to NICE's final appraisal (and despite a number of appeals from the manufacturer of the drug, clinical groups and patient associations), Tarceva® can only be used as a second or third line therapy in the treatment of NSCLC patients, when docetaxel is not an option. Nevertheless, clinicians advocate the use of Tarceva® in non-smokers, who seem to experience a very good drug response.	With more results from clinical trials, it might be that NICE will have to retract o its decision and widen the indications of Tarceva®.	More clinical trials would need to be undertaken in order to: - Prove that Tarceva® is a better option for NSCLC patients than existing treatments. - Prove that Tarceva® can be co-developed together with a genetic test (such as a test that analyses EGFR mutations implicated in drug response).

Existing UNCERTAINTIES and CONTROVERSIES that hamper the diffusion of PGx into clinical practice.		What is possible for PGx service delivery?	Due to the present situation, what is feasible for PGx service delivery?	Informing future policy options: what is desirable? How can PGx delivery in the NHS be improved?
General PGx Uncertainties	"Minibusters" will replace "Blockbusters"	It is possible that "minibusters" will be a way of introducing safer drugs into the market, or rescuing drugs that have been withdrawn from the market for safety reasons. It is, however, less likely that "minibusters" will replace existing "blockbusters" whose patents are still valid.	It is feasible that pharmaceutical companies may use PGx as a way of improving efficacy but also drug sales. It is not very feasible at the moment to invest in PGx for off-patent drugs.	Implement the use of PGx when there is a benefit for the patient. Develop incentives for investing in PGx for off-patent drugs.
	Organisational re-structuring of health service delivery	PGx will lead to a new re-structuring of health service delivery, provided the necessary mechanisms for testing (e.g. new laboratories, clinical guidelines, electronic medical records, PGx learning programmes) are put in place.	At the moment it is only feasible to offer PGX in a rather disorganised way (due often to a lack of consensus among clinicians and regulators).	- Develop stronger clinical expertise in genetics, so that the medical profession can fully grasp the benefits of PGx. - Establish protocols that coordinate genetic testing with genetic counselling and drug prescription.
	Informed Consent and future use of samples	It is possible to develop informed consent protocols where patients are given clear information about where their samples are going to be stored and for which purpose they might be used.	It might be feasible to develop "more informed" consent protocols, provided that new regulations request this.	- Ensure that, in every genetic procedure, informed consent is obtained and patients are informed of any type of analysis that their samples may be the subject of, either at present or in the future. - Strengthen the mechanisms of data protection when analysing and storing blood or DNA samples.

Existing UNCERTAINTIES and CONTROVERSIES that hamper the diffusion of PGx into clinical practice.		What is possible for PGx service delivery?	Due to the present situation, what is feasible for PGx service delivery?	Informing future policy options: what is desirable? How can PGx delivery in the NHS be improved?
General PGx Controversies	IPRs, Gene Patenting and service delivery	It might be possible t develop stronger regulations that control how gene patenting affects public service provision.	At the moment it is not possible to prevent patent holders from preventing public service providers from offering certain services associated with their patents.	-Enhance the collaboration between public research groups and private companies to favour scientific discoveries and PGx applications. -Enhance the current legal frameworks through which patenting can restrict access to public service delivery.

Table 7.2: PGx Policy Analysis and possible options for PGx service delivery

Annex 6 – Summary of the case studies

	TPMT Testing Service in UK
What does the test cover?	Measurement of the levels of TPMT enzyme (phenotyping), combined with full blood monitoring and liver function tests.
	Search for TPMT polymorphisms (*2,*3A, *3B and*3C) (genotyping), combined with full blood monitoring and liver function tests.
What are the benefits?	Prevention of TPMT-related ADRs and improvement in the management of patients with autoimmune diseases and ALL.
What are the disadvantages?	There still needs to be alternative blood monitoring tests and liver function tests to assess drug response.
	It is not reimbursed by the NHS. The test is implemented locally and local NHS Trusts run with the costs.
	There is not commercial interest in the test.
Who offers the test?	NHS Reference Laboratories.
How is the Service Provided?	As a Home Brew Test.
	It is the clinician who decides on therapy on the basis on TPMT results.
How is it Regulated?	The laboratories offering the test are accredited by CPA and NEQAS and comply with the European quality assurance standards, although they do not belong to the UKGTN (UK Genetics Testing Network).
How is it used?	Professional guidelines (in dermatology, rheumatology and gastroenterology) and peer review oversight plays an important role in the lack of formal guidelines.
Why was a TPMT service set-up?	After the Department of Health published a White Paper where it announced funding for genetics and PGx.

Summary of TPMT testing service in the UK

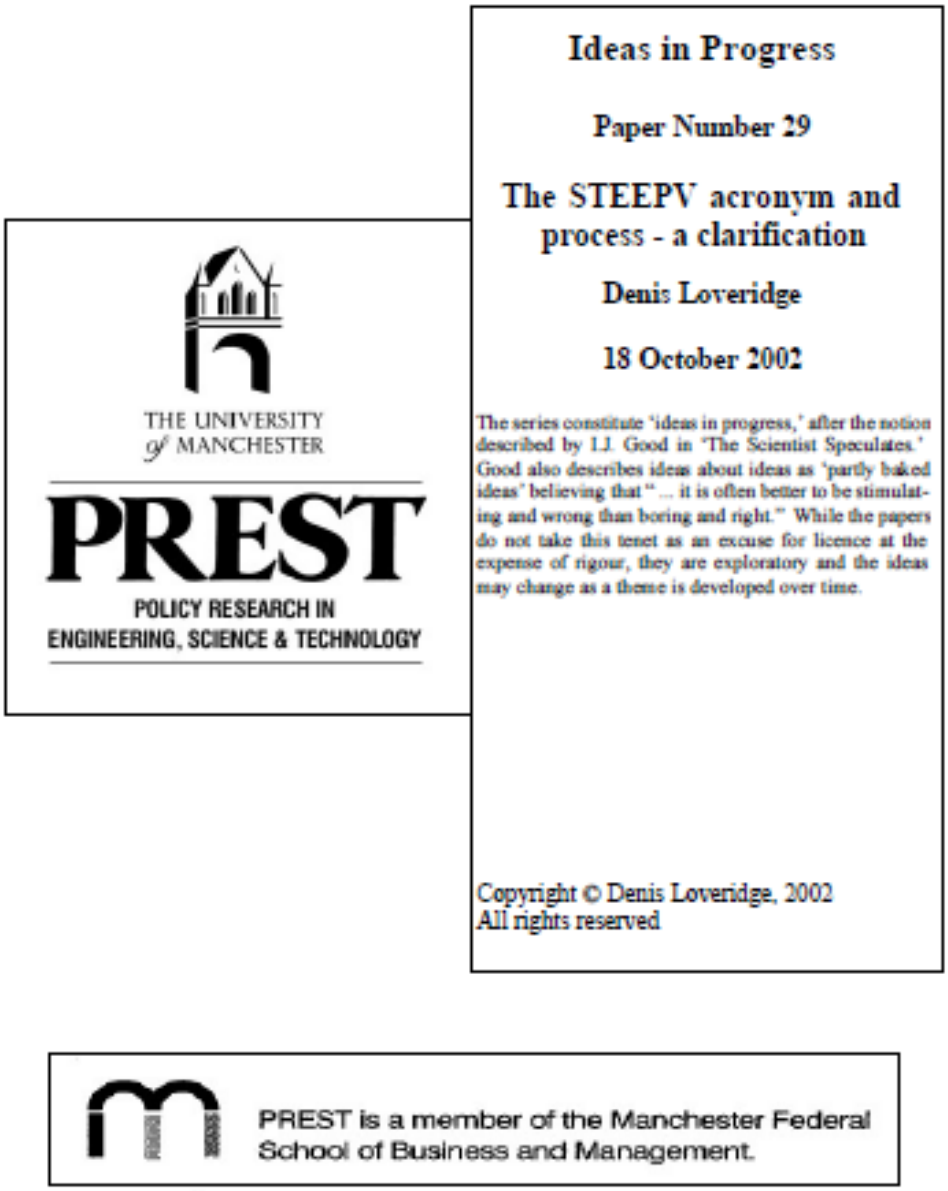
TPMT Testing Service in Spain	
What does the test cover?	Measurement of the levels of TPMT enzyme (phenotyping), combined with full blood monitoring and liver function tests.
	Search for TPMT polymorphisms is not a routine practice, although a pharmacogenetics laboratory is piloting TPMT genetic test.
What are the benefits?	Prevention of TPMT-related ADRs and improvement in the management of patients with inflammatory bowel disease, mainly, as well as some autoimmune neurological conditions such as multiple sclerosis.
What are the disadvantages?	There still needs to be alternative blood monitoring tests and liver function tests to assess drug response.
	There is not yet a wide knowledge about the benefits of the test and, as a consequence, its level of implementation is “irregular”.
Who offers the test?	UCB Pharma through a clinical trial at the beginning and, later on a private laboratory: Cerba International..
How is the Service Provided?	As a Home Brew Test.
	It is the clinician who decides on therapy on the basis on TPMT results.
How is it Regulated?	Cerba Internacional, the laboratory offering the test is an accredited laboratory that meets the European standards of quality (ISO9001)
How is it used?	There are no professional guidelines. TPMT testing is used according to the criteria of the clinician who prescribes azathioprine.
Why was a TPMT service set-up?	After UCB Pharma decided to start a clinical trial that assessed patient’s response to azathioprine according to the levels of TPMT in the blood.

Summary of TPMT testing service in Spain

EGFR Testing Service in UK	
Aims of the Test	EGFR testing is not implemented in clinical practice; it is only used for investigational purposes. There are not yet sufficient associations between mutations in the EGFR gene and response to Tarceva®.
How is NSCLC treated?	Chemotherapy and docetaxel are used as first and second line treatments. Tarceva® is only used as second line treatment when docetaxel is not an option and also, as a third line treatment.
	Iressa® has not been approved in the UK
How is Tarceva® regulated?	By NICE technology appraisals and clinical guidance, which advocate their use as second and third line therapies.
What are the benefits of "personalising" the use of Tarceva®?	NICE has suggested frther research based on sub-populations. It is, however, unceryain whether these sub-populations would be selected on the basis of mutations on the EGFR gene or taking into consideration other phenotypic characteristics.
What are the disadvantages and advantages of Tarceva®?	Patients can experience ADRs when taking Tarceva®, although the drug has advantages: it is administered in tablets and therefore, avoids hospitalisations. Also, some clinical results show that the drug is highly efficient in non-smolers, although, the prescription of Tarceva® in cases that lie out of the recommendations of NICE guidelines, are responsibility of clinical oncologists treating NSCLC patients.

Summary of EGFR testing service in the UK

Annex 7 – The STEEPV Accronym



THE UNIVERSITY of MANCHESTER

PREST

POLICY RESEARCH IN ENGINEERING, SCIENCE & TECHNOLOGY

Ideas in Progress

Paper Number 29

The STEEPV acronym and process - a clarification

Denis Loveridge

18 October 2002

The series constitute 'ideas in progress,' after the notion described by I.J. Good in 'The Scientist Speculates.' Good also describes ideas about ideas as 'partly baked ideas' believing that " ... it is often better to be stimulating and wrong than boring and right." While the papers do not take this tenet as an excuse for licence at the expense of rigour, they are exploratory and the ideas may change as a theme is developed over time.

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The STEEPV process evolved from ideas developed by Johnson Research Associates (JRA) in the early 1960s. These ideas were developed into the field anomaly relaxation (FAR) method in a collaborative arrangement between Stanford Research Institute, as it then was, and JRA, the outcome being published in 1971[1]. If the FAR method was the roots of the method, it was Schwartz[2], in work for the for a major US corporation, who evolved the STEPV process in the early 1970s; this was extended by Holroyd & Loveridge[3] in 1975 into STEEPV. So much for history, but what does STEEPV mean, what is the process and when has it been used?

STEEPV is an acronym for the six themes for thinking about the future:

Social
Technology
Economics
Ecology
Politics
Values

The second E (ecology) is often misinterpreted as "the environment." Ecology is a far wider concept being the relation between an organism and its environment. In this instance the organism is the human being and the environment is the totality of the world, both natural and human, in which human beings live. Consequently, the second E spans from say, the ecology of ideas to relations between human beings and the physical and biological system within which they live.

While not its original purpose, the acronym has been used as a guide to brainstorming sessions. There is nothing wrong in this but it should not be confused with the STEEPV process which is deeper and more arduous. The acronym has also been used to give structure to the learning processes that are essential to technology (TA) and environmental impact assessment[4] (EIA), to foresight and to scenario planning[5]. Here again the acronym acts as a guide to thinking and learning that inform the investigative processes of TA and EIA, and that underpin foresight and scenario planning.

Here I can only indicate the formal STEEPV process. It best used by a close knit group meeting very frequently to work with a complex set of 'mini-scenarios' each of which describes a particular direction of change or an end state or both. There are several sets of mini-scenarios under each letter of the acronym with up to seven elements in each mini-scenario set. The group process is judgmental, with the group seeking to agree or disagree which of the mini-scenarios in each set represent the 'hoped for world' by contrast with the 'real world' that is likely to exist at the time horizon of the study. Where a majority consensus exists, the descriptor of the mini-scenario set is taken to be a crucial issue or crisis in the Greek meaning of a turning point. The underlying learning programme (already referred to) provides detail insights as to why the choices have occurred and point toward further essential learning to enable to crisis to be further developed for larger-scale scenario development or simply to enable the consensual issues to be worked with for policy processes.

I know of two occasions when the process has been used. One by Schwartz the other in a major UK based international company (Holroyd & Loveridge), both occurrences were in the early to mid-1970s. In the latter, the group identified the following crises for the UK in the period up to the turn of the century as likely to influence the business environment:

1 socio-cultural change
2 socio-cultural pluralism
3 organization style
4 economic performance within the UK
5 economic performance by the UK overseas
6 technological innovation emphasis
7 psychological
8 urbanization
9 population growth or decline
10 domestic law and order
11 government domestic spending

12 social morality sanctions base

All of these crises were bound up with living and working conditions as part of the business environment.

Notes and references

1. Rhynne, R.F. et al, 'Projecting whole-body future patterns - the field anomaly relaxation (FAR) method,' SRI Educational Policy Res. Center, EPRC 6747-10 prepared for National Center for Res. and Dev., US Office of Education, 1971
2. Schwartz, P. Private communication, 1974
3. Holroyd, P. & Loveridge, D. Private communication, 1975
4. Loveridge, D. 'Technology and environmental impact assessment: methods and synthesis,' Int. J. Technology Management, 11, 5/6, 539-53, 1996
5. Loveridge, D. 'Scenarios,' Open University Business School, Course B885 'The challenge of the external environment,' Supplementary Reading Book 1, 1992